COMMONWEALTH OF AUSTRALIA

(Patents Act 1990)

IN THE MATTER OF: Australian Patent Application 696764 (73941/94). In the name of: Human Genome Sciences Inc.

- and -

IN THE MATTER OF: Opposition thereto by Ludwig Institute for Cancer Research, under Section 59 of the Patents Act.

STATUTORY DECLARATION

I, **Nicholas Kim Hayward** of The Human Genetics Laboratory, Queensland Institute of Medical Research, Herston, QLD 4029, Australia, a research scientist, declare as follows:

1.1. I have been asked by the Patent Attorneys representing Human Genome Sciences ("HGS") to serve as a scientific consultant in connection with the Ludwig Institute for Cancer Research Opposition to the issuance of HGS Australian Patent Application 696764, in the name of HGS, entitled: "Vascular Endothelial Growth Factor-2" ("the HGS patent specification").

1.2. In acting as a scientific consultant for HGS, I provided a Statutory Declaration executed December 8, 2000 ("Hayward Declaration 1") in connection with the Opposition of the HGS patent specification, in which I provided my comments and opinions on what the HGS patent specification would have disclosed and described to me as a researcher working in the field of the molecular biology of growth factors in Australia in March 1994, which I understand is the earliest

WRAY & ASSOCIATES
Patent & Trade Mark Attorneys

6th Floor, GHD House
239 Adelaide Terrace, Perth
Western Australia 6000
Australia

Tel: (618) 9325 6122
Fax: (618) 9325 2883
Email: wray@wray.com.au
Our Ref: GBC: 100868

priority date of the HGS patent specification. I also provided comments and opinions on the experimental evidence provided in Dr. Alitalo's Statutory Declaration executed on 15 February 2000 ("Alitalo Declaration 1").

Alitalo Declaration 2

1.3. I have been asked by the Patent Attorneys representing HGS to review and provide my comments and opinions on the Statutory Declaration executed by Dr. Alitalo on 14 September 2001 ("Alitalo Declaration 2").

1.4. When I read VEGF-2 in the HGS patent specification I understood it to be referring to VEGF-C. These names are alternate nomenclature for the same protein.

New experiments presented in Alitalo Declaration 2

1.5. The new experiments presented in Alitalo Declaration 2 are flawed for the following reasons:

- Dr Alitalo does not take account of all of the information presented in the HGS patent specification. None of his experiments report on the effect of attaching a heterologous signal sequence to the 350 amino acid VEGF-2 sequence. This is discussed more fully in paragraph 1.7 below.
- Dr. Alitalo does not provide appropriate positive and negative controls for the expression experiments.
- No experiments were conducted nor were results produced concerning the transfection efficiency of the plasmids used in the experiments. The transfection efficiency will directly correlate with the level of protein expression detected.
- No data is presented concerning parameters such as cell densities or growth conditions all of which can affect the transfection efficiency of expression constructs into cells.
- The experimental protocol described in Alitalo Declaration 2 does not allow for detection of VEGF-2 protein expression over various time points. Rather, protein levels are assessed fifty hours post-transfection (forty-eight hours and overnight metabolic labelling). Without measuring for VEGF-2 expression over various time points, it is not possible to detect

VEGF-2 that has been expressed and purportedly degraded over time.

Consequently, Dr Alitalo's experiments do not, in my opinion provide any meaningful conclusions regarding the expression, processing and secretion of VEGF-2 as disclosed in the HGS patent specification.

1.6. In designing new experiments, Dr Alitalo seems to have ignored the fact that the HGS patent specification clearly discloses the utilisation of a heterologous signal sequence capable of directing secretion of the translated protein (see, the HGS patent specification at page 14, lines 6-23). Further, in designing these identified experiments Dr Alitalo seems to have completely ignored my comments in Hayward Declaration 1 (see for example paragraph 3.19) where I emphasised that the use of a heterologous signal sequence in the production of VEGF-2 is something I ***could*** and ***would*** have attempted in March 1994 had the VEGF-2 sequence reported in the HGS patent specification not been secreted following properly controlled expression experiments. Nothing in Alitalo Declaration 2 has led me to change this opinion. In my opinion the HGS patent specification provides all of the information that I would have required to produce VEGF-2 in its mature form.

Paragraphs 3.7 and 5.5

1.7. In paragraphs 3.7 and 5.5 of Alitalo Declaration 2, Dr Alitalo appears to me to suggest that one would not expect to achieve processing of the 350 amino acid sequence disclosed in the HGS patent specification. The processing of a protein such as VEGF-2 is determined by its amino acid sequence. In the absence of any evidence to the contrary I would have proceeded in March 1994 on the basis that the 350 amino acid sequence of VEGF-2 contained all the necessary information and signals required by a host cell to process the amino acid sequence to its mature form. By March 1994 I was aware that any given host cell would possess the proteolytic enzymes and cellular machinery to naturally process a protein such as VEGF-2 to its mature form. I was also aware that post translational processing of an amino acid sequence is a natural and inherent property of the expression and secretion of a protein from a host cell.

Paragraphs 4.1 to 4.3

1.8. In paragraphs 4.1 to 4.3 of Alitalo Declaration 2, Dr Alitalo alleges that the VEGF-2 clone deposited with the American Type Culture Collection as ATCC Accession Number 75698 does not contain the complete 350 amino acid sequence when compared to the sequence set forth in Figure 1 of the HGS patent specification. Had I been presented with the HGS patent specification in March 1994, I would not have needed the deposit to isolate the 350 amino acid coding sequences for VEGF-2. Rather, I would have isolated the sequence from a suitable library (such as that mentioned in the HGS patent specification at page 5, lines 19-26) or from RNA from the sources provided by the HGS patent specification (page 5, lines 19-24, Example 1 and Figure 5) using the information in Figure 1 of the HGS patent specification. By March 1994 techniques such as PCR, were routinely available for achieving this objective and were commonly used in my laboratory for isolating nucleotide sequences. An additional approach would be to synthesize a double stranded oligonucleotide containing the missing sequence and ligate the oligonucleotide to the DNA obtained from the ATCC deposit. Such research was entirely routine by March 1994. Thus, in my opinion, the information that I would have relied upon to isolate the 350 amino acid sequence is that derived from Figure 1 in the HGS patent specification, which would have been sufficient for me or other skilled molecular biologists to isolate the sequence.

Paragraph 5.6

1.9. In paragraph 5.6 of Alitalo Declaration 2, Dr Alitalo mentions for the first time that the HGS patent specification does not disclose the molecular weight of the mature form of VEGF-2. Neither I nor my colleagues who were working with PDGF/VEGF family members in Australia in March 1994 would have required this information from the HGS patent specification to produce and recognize a mature form of the protein. Regardless, using the HGS patent specification I and I believe my colleagues could have easily expressed and secreted the protein and then measured the molecular weight of the secreted and processed forms of the protein. Had we done this, we would have identified the molecular weight of the mature form of VEGF-2, as the

molecular weight is an intrinsic and natural property of the processing of the protein. The gathering of such information was an entirely routine practice for molecular biologists in Australia by March 1994.

1.10. In paragraph 5.6 of Alitalo Declaration 2, Dr Alitalo suggests that the experiments reported by Dr Powers should be ignored because they are "unrelated" to the teachings in the HGS patent specification. In reaching this conclusion, Dr Alitalo seems to have ignored the fact that the HGS patent specification clearly discloses the utilisation of a heterologous signal sequence capable of directing secretion of the translated protein (see, the patent specification at page 14, lines 6-23). I have been presented with a copy of (a) Susan Powers Declaration dated 13 December 2000 ("Power Declaration 1") and (b) Susan Powers Declaration dated 22 March 2002 ("Power Declaration 2") and note that they both demonstrate that a 350 amino acid form of VEGF-2 could be expressed, processed and secreted. The methodology used to carry out the experiments described and performed by Dr Powers in both Power Declaration 1 and Power Declaration 2 are, in my opinion, the types of experiments that I and I believe any molecular biologist of ordinary skill in Australia would have performed in March 1994, when presented with the patent specification.

Aaronson Declaration 2

1.11. The Patent Attorneys representing HGS have also presented to me a second Declaration by Professor Stuart Aaronson dated 22 March 2002 ("Aaronson Declaration 2") commenting, *inter alia*, on Alitalo Declaration 2. I have read and understood Aaronson Declaration 2 and its annexed documents.

1.12. My separate comments and observations concerning Alitalo Declaration 2 are provided above. These comments and observations are, I believe, consistent with those made by Professor Aaronson in Aaronson Declaration 2. Thus, I am in complete agreement with the opinions expressed by Professor Aaronson in his Declaration.

AND I make this solemn declaration by virtue of the Statutory Declarations Act, 1959 and subject to the penalties provided by that Act for the making of

false statements in statutory declarations, conscientiously believing the statements contained in this declaration to be true in every particular.

DATED this day Twenty Sixth of March 2002.

DECLARED at: Brisbane, Queensland)
BEFORE me: NERIDA FOX)

N. Hayward

Nicholas Kim Hayward

Witness

COMMONWEALTH OF AUSTRALIA

IN THE MATTER OF: Australian Patent Application 696764 (73941/94). In the name of: Human Genome Sciences Inc.

-and-

IN THE MATTER OF: Opposition thereto by Ludwig Institute for Cancer Research, under Section 59 of the Patents Act.

STATUTORY DECLARATION

I, Susan Power of Cell & Molecular Technologies, Inc., Phillipsburg, New Jersey, United States of America, declare as follows:

1. At the request of the Patent Attorneys representing Human Genome Sciences ("HGS") in connection with the Ludwig Institute for Cancer Research Opposition to the issuance of HGS Australian Patent Application 696764, in the name of HGS, entitled: "Vascular Endothelial Growth Factor-2" ("the HGS patent specification"), I performed certain experiments as described in a Statutory Declaration executed December 13, 2000 ("Power Declaration I"). The Patent Attorneys representing HGS have now requested that I provide additional information regarding those experiments and carry out additional experiments.

2. In particular, I have been asked to clarify the construction of the expression vectors described in Power Declaration I used to determine whether the 350 amino acid form of VEGF-2 fused in frame with a heterologous signal sequence would result in the expression and secretion of the protein from eukaryotic cells.

3. The Patent Attorneys representing HGS have requested that I perform additional experiments to determine whether the VEGF-2 coding sequence contained in ATCC Deposit No. 75698 fused in frame with a heterologous signal sequence would result in the expression and secretion of the protein

from eukaryotic cells. Further, the Patent Attorneys representing HGS have requested that I construct an expression vector containing the 350 amino acid form of VEGF-2 fused in frame with a heterologous signal sequence using only the VEGF-2 coding sequence contained in the ATCC Deposit No. 75698 and the nucleotide sequence of Figure 1 of the HGS application which contains a nucleotide sequence encoding the 350 amino acid form of VEGF-2, and methods and materials known as of March, 1994. I have done this and the experiments I have conducted are described herein.

The Design and Construction of the Expression Vectors Used in the Experiments Described in Power Declaration I

4. The Patent Attorneys representing HGS had previously asked that I perform experiments in order to determine whether the 350 amino acid form of VEGF-2 would be secreted from cells when attached to a heterologous signal sequence. To achieve this aim, I transfected eukaryotic cells with expression vectors encoding either (1) the 350 amino acid form of VEGF-2 fused in frame with a heterologous signal sequence, or (2) the 419 amino acid form of VEGF-2. The transfected cells were grown and allowed to express the gene products encoded by the vectors. At various time points, both the cell lysates and culture medium were assayed for the presence of VEGF-2 protein. The presence of VEGF-2 protein in either the cell lysates or culture medium was determined by Western Blot analysis of the samples. I have reviewed my notebooks documenting the experiments I performed to achieve the aims of the experiments described in Power Declaration I and provide the following details:

5. For the experiments in Power Declaration I, I was asked to obtain the VEGF-2 DNA directly from the American Tissue Culture Collection (ATCC). I did not obtain any constructs from HGS. The only VEGF-2 clones I obtained were ATCC Deposit No. 97149 and ATCC Deposit No. 75698. The Patent

Attorneys representing HGS provided to me Figure 1 of the HGS patent specification which contains a nucleotide sequence of the 350 amino acid form of VEGF-2. The HGS Patent Attorneys also provided to me the nucleotide sequence of the 419 amino acid form of VEGF-2. It was my understanding that a nucleotide sequence encoding the 350 amino acid form of VEGF-2 was contained in ATCC Deposit No. 75698 and the nucleotide sequence encoding the 419 amino acid form of VEGF-2 was contained in ATCC Deposit No. 97149. It was also my understanding that the amino acid sequence of the 350 amino acid form of VEGF-2 corresponds to residues 70 to 419 of the 419 amino acid form of VEGF-2.

6. As I was under significant time constraints to complete the experiments, I elected to generate the DNA for the expression constructs using only the clone contained in ATCC Deposit No. 97149. Because I was using ATCC Deposit No. 97149 to generate the DNA, I also consulted the nucleotide sequence information relating to the 419 amino acid form of VEGF-2. I considered this to be a reasonable approach since the coding sequences for both the 419 and 350 amino acid forms of VEGF-2 are contained in ATCC Deposit No. 97149. Thus, I isolated the nucleotide sequences encoding the 419 amino acid form of VEGF-2 as well as the 350 amino acid form of VEGF-2 using ATCC Deposit No. 97149 as the sole source of VEGF-2 coding sequences.

7. My understanding of the goals of the experiments described in Power Declaration I was to demonstrate that the 350 amino acid form of VEGF-2 could be successfully expressed and secreted when expressed as taught by the HGS patent specification, *i.e.*, using a heterologous signal sequence. I did not inform the patent attorneys representing HGS at the time of carrying out these experiments nor at the time of signing Power Declaration I that I had isolated the 350 amino acid form of VEGF-2 from the ATCC Deposit No. 97149 clone. It was only when they asked on or about September 24, 2001 for

further clarification of the experiments that I conducted that I informed them of these details.

8. I have now been asked to redesign my experimental protocol to specifically use the VEGF-2 coding sequence contained in ATCC Deposit No. 75698 to generate the expression construct containing the 350 amino acid form of VEGF-2. I have been asked that I perform the experiments using the VEGF-2 coding sequence contained in ATCC Deposit No. 75698 to determine whether the 350 amino acid form of VEGF-2 fused in frame with a heterologous signal sequence would result in the expression and secretion of the protein from eukaryotic cells.

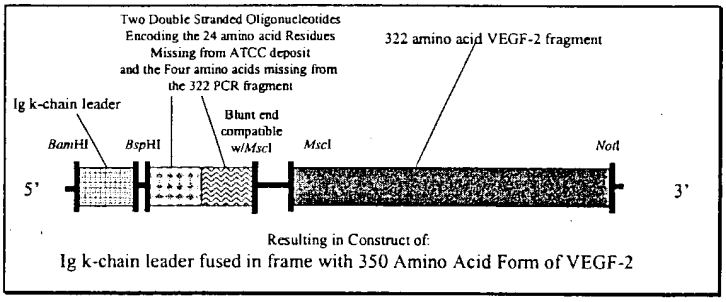
9. I have provided the Patent Attorneys for HGS with the details of a sequence analysis of the VEGF-2 coding sequence contained in ATCC Deposit No. 75698. The VEGF-2 clone contained in the ATCC Deposit No. 75698 lacks 24 amino acids at the N-terminal end of the 350 amino acid form of VEGF-2, and corresponds to residues 94 to 419 of the 419 amino acid form of VEGF-2, *i.e.*, a 326 amino acid form of VEGF-2. I have also been asked to perform experiments to determine if the 326 amino acid form of VEGF-2 as encoded by a nucleotide sequence contained in ATCC Deposit No. 75698 fused to a heterologous signal sequence would result in the expression and secretion of the protein from eukaryotic cells.

10. Even though ATCC Deposit No. 75698 lacks the complete coding sequence for the 350 amino acid form of VEGF-2, a molecular biologist as of March 1994 would be able to recreate the 350 amino acid form of VEGF-2 given the description of the complete sequence in the HGS patent specification (as described below) and that is the course I could have taken at that time and I would have expected other molecular biologists to have been able to do the same. I generated an expression vector containing the 350 amino acid form of VEGF-2 fused in frame with a heterologous signal sequence, using only the

ATCC Deposit No. 75698 and the sequence of Figure 1 in the HGS patent specification, and techniques and materials routinely known and used in the art as of March 1994.

The Expression Vector Containing the 350 Amino Acid Form of VEGF-2 Is Generated Using Only ATCC Deposit No. 75698 and Figure 1 of the HGS Patent Specification

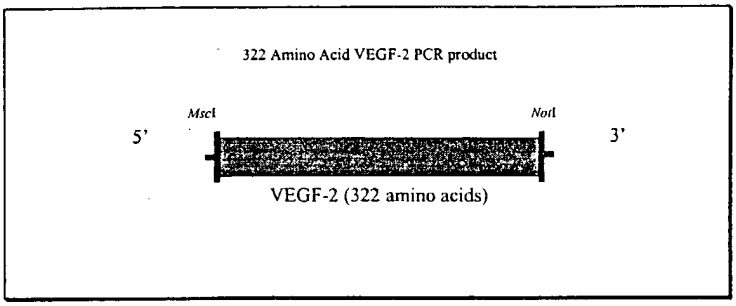
11. The general design of the expression vector containing the 350 amino acid form of VEGF-2 fused in frame with a heterologous signal sequence is as follows:



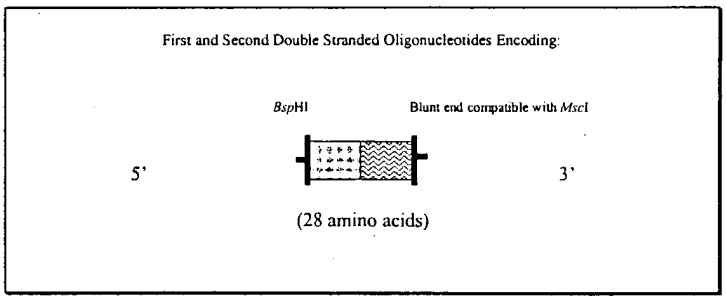
12. Since all that I had at my disposal were ATCC Deposit No. 75698 and Figure 1 of the HGS patent specification, I did the following:

12.1 First, I chose to directly isolate a nucleotide sequence encoding the C-terminal 322 residues of the 326 amino acid form of VEGF-2. The 322 residues corresponding to residues 98 to 419 of the 419 amino acid form of VEGF-2 were amplified by PCR from ATCC Deposit No. 75698. I chose to isolate a VEGF-2 fragment of 322 amino acids to facilitate the cloning of the VEGF-2 coding sequence in frame into the expression constructs. To do so, I designed primers based on the sequence provided in Figure 1 of the HGS patent specification, the sequence of ATCC Deposit No. 75698, and the sequence of restriction enzyme recognition sites, *e.g.*, *Msc*I and *Not*I. The resulting 322 amino

acid fragment of VEGF-2 amplified from ATCC Deposit No. 75698 was digested with *Msc* I and *Not* I.

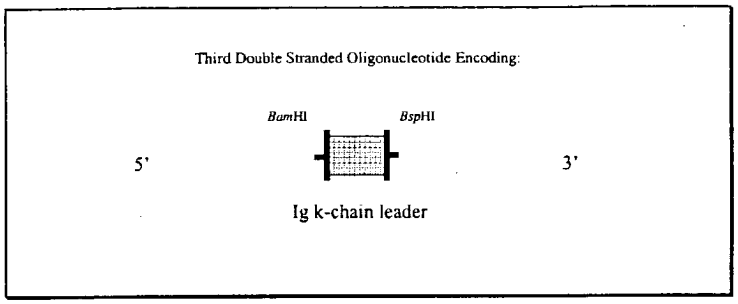


12.2 Using a nucleotide sequence encoding the 350 amino acid form of VEGF-2 contained in Figure 1 of the HGS specification, I designed two double stranded oligonucleotides to encode (once ligated together) a 28 amino acid VEGF-2 fragment. This fragment encompasses the 24 amino acids missing from ATCC Deposit No. 75698 and the additional 4 amino acids missing from the 322 amino acid fragment of the 326 form of VEGF-2. Specifically, once ligated together, the oligonucleotides were designed to result in the generation of a 28 amino acid fragment engineered to have a 5' end with a *Bsp*H I restriction site overhang and a 3' blunt end compatible with a *Msc* I restriction site as shown below. Methods and materials for generating such double stranded oligonucleotides were routine and known by March, 1994.



12.3 A third double stranded oligonucleotide encoding the secretion signal sequence of the Ig k-chain leader signal sequence that was also used in

the experiments described in Power Declaration I was engineered to contain a *Bam* HI restriction enzyme overhang at the 5' end and a *Bsp* HI restriction enzyme overhang at the 3' end as shown below. Ig k-chain leader signal sequence was a recognized signal sequence available as of March, 1994.



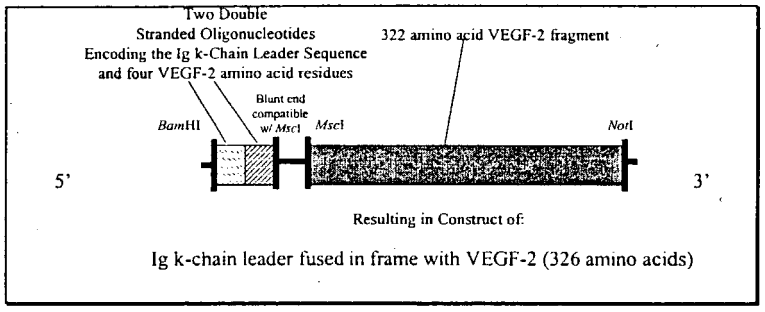
12.4 The 322 amino acid VEGF-2 fragment and the three double stranded oligonucleotides described above were ligated and subcloned at once into the *Not* I/*Bam* HI sites of the expression vector pCMV-I which was described in Power Declaration I. The resulting expression vector contains the construct as described in ¶ 11 above. The VEGF-2 sequence is under the control of a CMV-I promoter, a promoter routinely used as of March, 1994.

12.5 The resulting 350 amino acid form of VEGF-2 construct was sequenced and confirmed to be correct and is detailed in Appendix I.

13. The design of the expression vector containing the VEGF-2 coding sequence found in ATCC Deposit No. 75698 used in the study results in a construct with the 326 amino acid form of VEGF-2 linked to a heterologous sequence and is as follows:

14. To generate the construct, the 322 amino acid VEGF-2 fragment flanked with a *Msc* I site at the 5' end and the *Not* I site at the 3' end was generated as

described above (*see* ¶12.1). I designed two double stranded oliogonucleotides that once ligated together encoded the Ig k-chain leader signal sequence and the four amino acid residues corresponding to residues 94 to 97 of the 419 amino acid form of VEGF-2, *i.e.*, the first four residues of the 326 amino acid form of VEGF-2 of ATCC Deposit No. 75698 engineered to contain a 3' blunt end compatible with a *Msc*I restriction site and a 5' *Bam* HI site. The 322 amino acid VEGF-2 fragment was simultaneously fused in frame with the two double stranded oliogonucleotides, as shown below, and subcloned into the expression vector pCMV-I *Bam* HI/ *Not* I sites. Again, the VEGF-2 sequence is under the control of a CMV-I promoter, a promoter routinely used as of March 1994.



15. The sequence of the resulting 326 amino acid form of VEGF-2 construct was confirmed to be correct and is detailed in Appendix II, attached hereto.

16. For purposes of the following experiments, I used the expression vector encoding the 419 amino acid form of VEGF-2 described in Power Declaration I (*see* Power Declaration I ¶¶ 3 to 6).

17. As set out in Power Declaration I, the sequence of the construct was confirmed to be correct and is detailed in Appendix III, attached hereto.

Using Only the VEGF-2 Clone Contained in ATCC Deposit No. 75698 Fused in Frame with a Heterologous Signal Sequence, Expression and Secretion of VEGF-2 Is Achieved

18. The Patent Attorneys for HGS requested that I perform the following experiments in order to determine whether using only the 350 amino acid form or the 326 amino acid form of VEGF-2 contained in ATCC Deposit No. 75698 fused in frame with a heterologous signal sequence would result in the expression and secretion of VEGF-2 from eukaryotic cells.

19. The overall experimental design is as follows: eukaryotic cells were transfected with expression vectors encoding the 419 amino acid form of VEGF-2, the 350 amino acid form of VEGF-2 fused in frame with a heterologous signal sequence, or the 326 amino acid form of VEGF-2 fused in frame with a heterologous signal sequence. The transfected cells were cultured for 24 or 48 hours to allow for expression of the gene products encoded by each vector. In order to determine whether the VEGF-2 gene product was being expressed and secreted, the cell lysates and culture medium were collected to assay for the presence of VEGF-2. The presence of VEGF-2 in either the cell lysates or culture medium was determined by Western Blot analysis of the samples using a rabbit polyclonal antibody to VEGF-2 that recognizes all forms and fragments of VEGF-2. The same antibody was used in Power Declaration I to assay the presence of VEGF-2 proteins.

20. The three VEGF-2 constructs encoding the 419, 350 and 326 amino acid forms of VEGF-2 each were transiently transfected in duplicate, using the lipofectin method into the Human Embryonic Kidney cell line, HEK-293 tsA-0. The method of transfection and the cell line were both routinely used as of March, 1994. As a control for transfection efficiency, each construct was co-transfected with the vector pCMV-β-gal. The efficiency of transfection was determined by β-gal staining 48 hours after transfection. As a negative control,

the vector pCMV-I without the addition of any VEGF-2 coding sequences was transfected in parallel.

21. The transfection design is as follows:

6 dishes transfected with: pCMV-I-VEGF-419;

6 dishes transfected with: pCMV-I-signal sequence-VEGF-350;

6 dishes transfected with: pCMV-I-signal sequence-VEGF-326;

6 dishes transfected: pCMV-I;

1 dish transfected with: pCMV-I-VEGF-419 + pCMV-β-gal;

1 dish transfected with: pCMV-I-signal sequence-VEGF-350 + pCMV-β-gal; and

1 dish transfected with: pCMV-I-signal sequence-VEGF-326 + pCMV-β-gal.

22. After transfection, DMEM medium containing 3% serum was added to the cells. Aliquots of cell extracts and conditioned medium were prepared from each transfection at: T_0 hours, T_{24} hours and T_{48} hours, in duplicate.

23. At the time of harvesting the cells and medium were treated as follows:

Medium: Harvested medium was concentrated 3 fold using Centricon 10 concentrator devices. One volume of 2 x PAGE loading dye was added to each sample.

Cell Extracts: The cells were harvested by trypsinization and collected by centrifugation. The cell pellet was resuspended and lysed, and one volume of 2 x PAGE loading dye was added to each sample.

24. To determine the transfection efficiency, dishes transfected with the pCMV-β-gal construct were fixed and stained for β-gal activity 48 hours after transfection. All dishes were found to have the same percentage of transfected cells (70%).

25. Each protein sample was subjected to Western analysis as outlined below. Prior to loading on to a 12% (w/v) Tris-Glycine SDS-Polyacrylamide gel, the samples were boiled for 5 minutes and cooled on ice. The two end lanes of each gel contained the appropriately sized molecular weight markers to estimate the migration rate of proteins predicted to run in the 16 to 85 kDa size range. The samples were electrophoresed according to standard conditions.

26. Following electrophoresis, the samples were transferred to a PVDF membrane. Each membrane was blocked by a one hour incubation in phosphate buffered saline (PBS) containing 3% Bovine Serum Albumin (BSA). The blot was then incubated at 4°C in PBS containing 0.1% BSA and 500ng/ml of purified rabbit anti-VEGF-2 antibody, a polyclonal antibody which recognizes all immunogenic fragments of VEGF-2. After three 5 minute washes in PBS containing 0.1% Tween, the blot was incubated for 1 hour in PBS containing 0.1% BSA and a 1:3000 dilution of Goat Anti-Rabbit IgG Horse Radish Peroxidase (HRP) conjugated antibody. The blot was washed six times for 5 minutes in PBS containing 0.1% BSA. The blot was developed with 2ml/blot of ECL detection reagent (obtained from Amersham) for one minute and then exposed directly to Polaroid films for approximately 2-3 seconds.

27. The result of the experiment is shown in Figure 1, attached hereto. The samples included in the figure are as follows:

Immunoblot analysis of VEGF constructs transiently expressed in HEK293T cells

Lane	**Pellet/ Supernatant**	**Construct (419, 350, 326, or neg. control)**	**T (h) post-transfection**
Gel 1			
1	P	Negative control	24
2	S	Negative control	24
3	P	350-signal	24
4	S	350-signal	24
5	P	326-signal	24

6	S	326-signal	24
7	P	419	48
8	S	419	48
Gel 2			
1	P	Negative control	24
2	S	Negative control	24
3	P	350-signal	24
4	S	350-signal	24
5	P	326-signal	24
6	S	326-signal	24
7	P	419	48
8	S	419	48
Gel 3			
1	P	Negative control	24
2	S	Negative control	24
3	P	419	24
4	S	419	24
5	P	419	24
6	S	419	24
7	P	350-signal	48
8	S	350-signal	48
9	P	419	48
10	S	419	48
Gel 4			
1	P	Negative control	48
2	S	Negative control	48
3	P	350-signal	48
4	S	350-signal	48
5	P	326-signal	48
6	S	326-signal	48
7	P	326-signal	48
8	S	326-signal	48

9	P	419	48
10	S	419	48

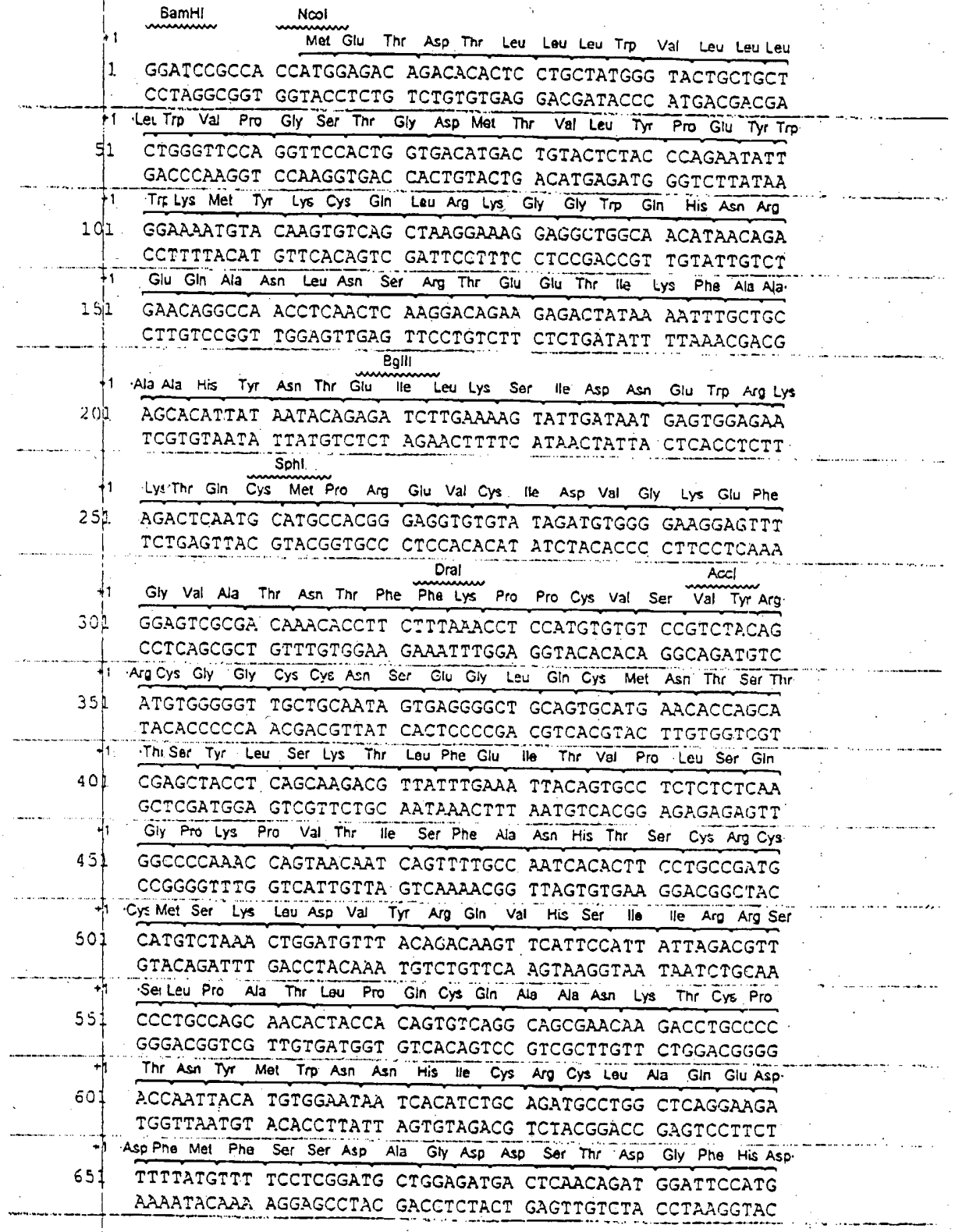
31. The Western Blot analysis indicates a broad band resolving at approximately 30kDa was present in the medium collected from the transfection of the 419 amino acid VEGF-2 construct, the 350 amino acid VEGF-2 signal sequence construct, and the 326 amino acid VEGF-2 signal sequence construct (see Figure 1, attached hereto as Appendix IV). The secreted protein was visible at 24 hours and 48 hours after transfection. The secreted product from cells containing the 419 amino acid VEGF-2 construct, the 350 amino acid VEGF2 signal sequence construct, and the 326 amino acid VEGF-2 signal sequence construct are all the same approximate size.

AND I declare that all the statements made in this Declaration are of my own are true in every particular, and that all statements made on information and belief are believed to be true.

Sworn by the said Susan Power, Susan Power at Phillipsburg, New Jersey, on this 22nd day of March 2002;
before me Gean Rotmistrenko
Notary Public

GEAN ROTMISTRENKO
Notary Public, State of New York
No. 41-4778718
Qualified in Queens County
Certificate Filed in New York County
Commission Expires October 31, 2005

VEGF-350+Signal



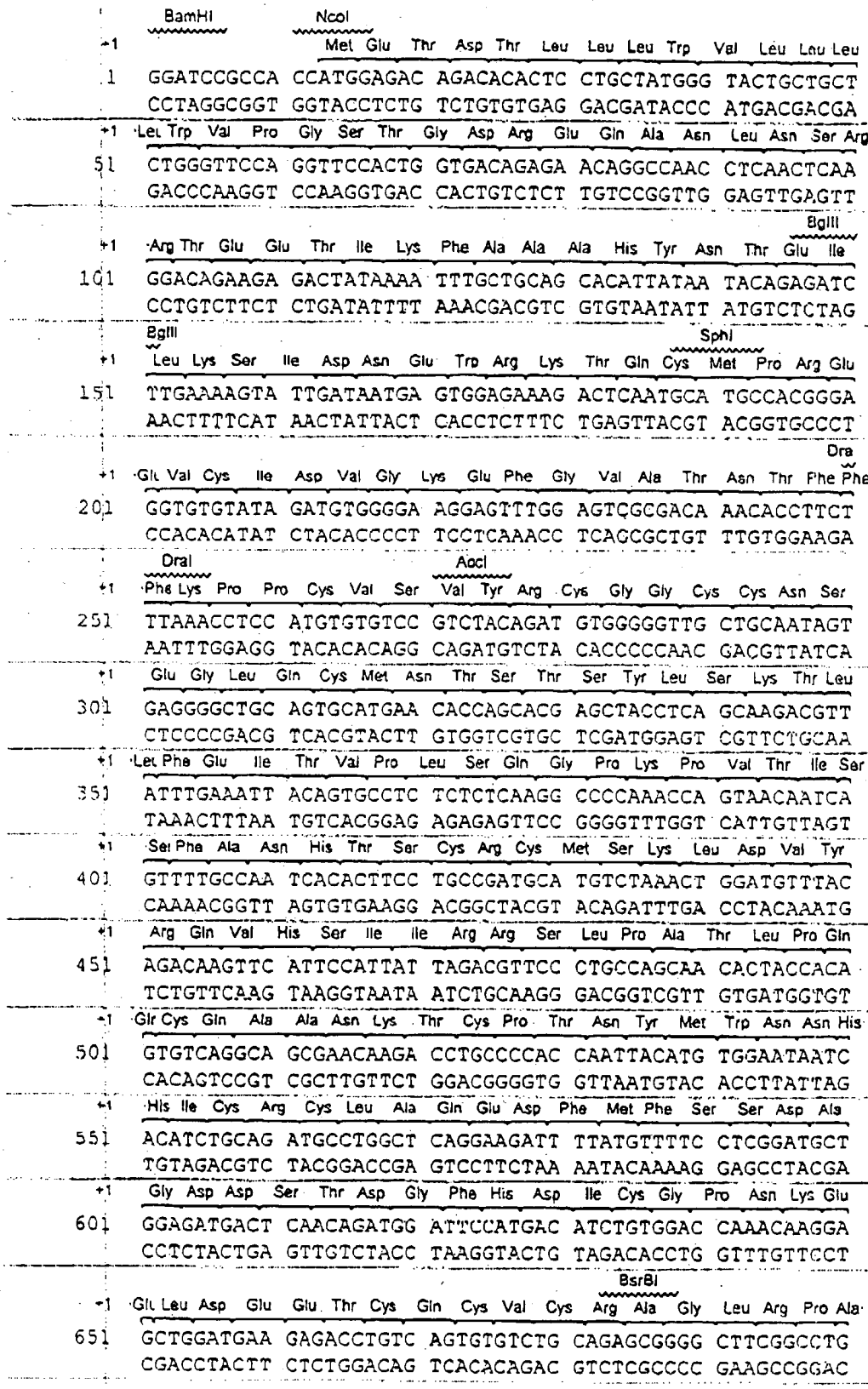
POWER DECLARATION II

APPENDIX I

VEGF-350+Signal

```
    +1  Asp Ile Cys Gly Pro Asn Lys Glu Leu Asp Glu Glu Thr Cys Gln Cys Val
701 ACATCTGTGG ACCAAACAAG GAGCTGGATG AAGAGACCTG TCAGTGTGTC
    TGTAGACACC TGGTTTGTTC CTCGACCTAC TTCTCTGGAC AGTCACACAG

                Bsr8I
    +1  Cys Arg Ala Gly Leu Arg Pro Ala Ser Cys Gly Pro His Lys Glu Leu Asp
751 TGCAGAGCGG GGCTTCGGCC TGCCAGCTGT GGACCCCACA AAGAACTAGA
    ACGTCTCGCC CCGAAGCCGG ACGGTCGACA CCTGGGGTGT TTCTTGATCT

    +1  Asp Arg Asn Ser Cys Gln Cys Val Cys Lys Asn Lys Leu Phe Pro Ser Gln Cys
801 CAGAAACTCA TGCCAGTGTG TCTGTAAAAA CAAACTCTTC CCCAGCCAAT
    GTCTTTGAGT ACGGTCACAC AGACATTTTT GTTTGAGAAG GGGTCGGTTA

    +1  Cys Gly Ala Asn Arg Glu Phe Asp Glu Asn Thr Cys Gln Cys Val Cys Lys
851 GTGGGGCCAA CCGAGAATTT GATGAAAACA CATGCCAGTG TGTATGTAAA
    CACCCCGGTT GGCTCTTAAA CTACTTTTGT GTACGGTCAC ACATACATTT

    +1  Arg Thr Cys Pro Arg Asn Gln Pro Leu Asn Pro Gly Lys Cys Ala Cys Glu
901 AGAACCTGCC CCAGAAATCA ACCCCTAAAT CCTGGAAAAT GTGCCTGTGA
    TCTTGGACGG GGTCTTTAGT TGGGGATTTA GGACCTTTTA CACGGACACT

    +1  Glu Cys Thr Glu Ser Pro Gln Lys Cys Leu Leu Lys Gly Lys Lys Phe His His
951 ATGTACAGAA AGTCCACAGA AATGCTTGTT AAAAGGAAAG AAGTTCCACC
    TACATGTCTT TCAGGTGTCT TTACGAACAA TTTTCCTTTC TTCAAGGTGG

    +1  His Gln Thr Cys Ser Cys Tyr Arg Arg Pro Cys Thr Asn Arg Gln Lys Ala
1001 ACCAAACATG CAGCTGTTAC AGACGGCCAT GTACGAACCG CCAGAAGGCT
    TGGTTTGTAC GTCGACAATG TCTGCCGGTA CATGCTTGGC GGTCTTCCGA

    +1  Cys Glu Pro Gly Phe Ser Tyr Ser Glu Glu Val Cys Arg Cys Val Pro Ser
1051 TGTGAGCCAG GATTTTCATA TAGTGAAGAA GTGTGTCGTT GCGTCCCTTC
    ACACTCGGTC CTAAAAGTAT ATCACTTCTT CACACAGCAA CGCAGGGAAG

                                        NotI
                                        EagI
    +1  Ser Tyr Trp Lys Arg Pro Gln Met Ser ---
1101 ATATTGGAAA AGACCACAAA TGAGCTAAGC GGCCGCG
    TATAACCTTT TCTGGTGTTT ACTCGATTCG CCGGCGC
```

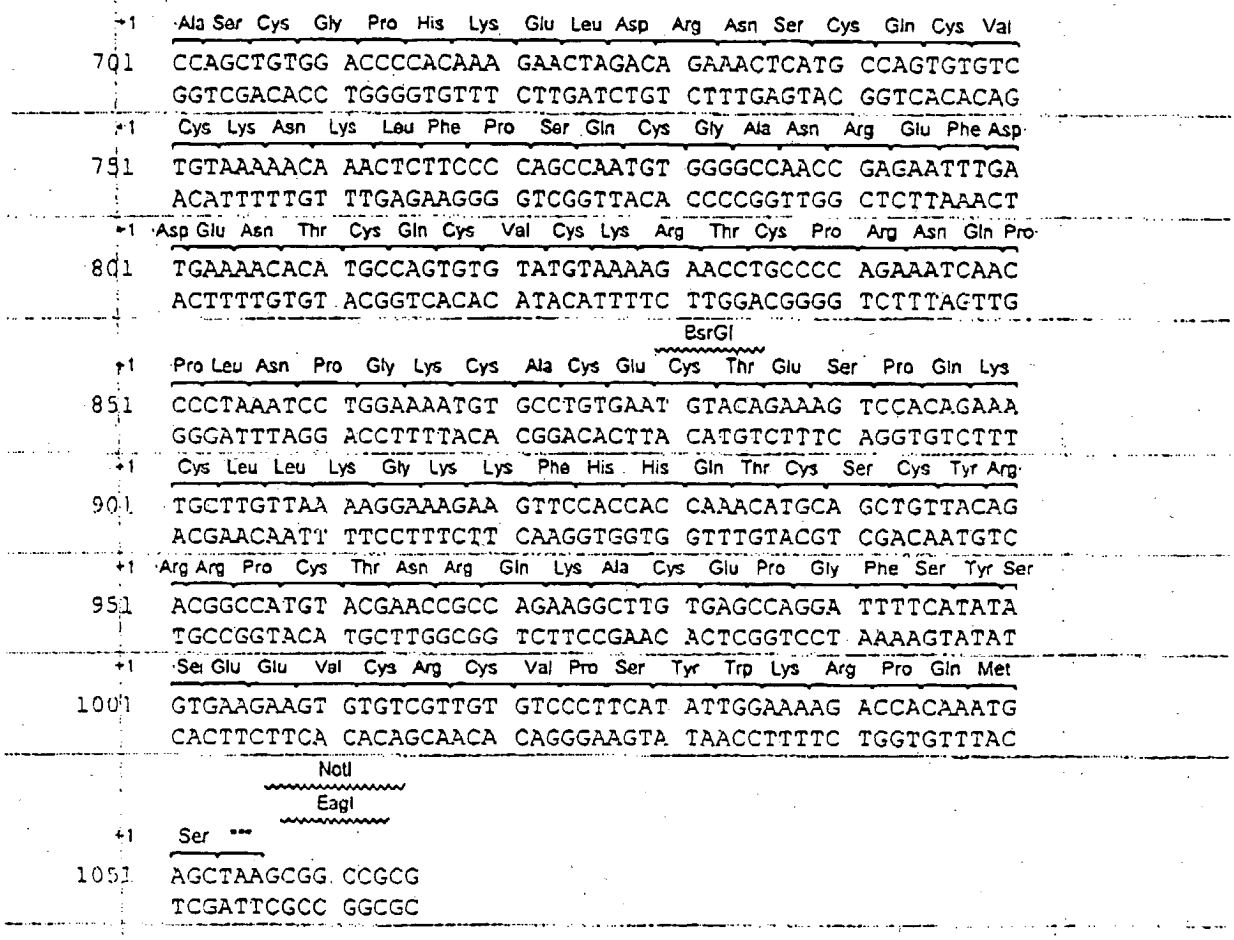
VEGF 326+Signal

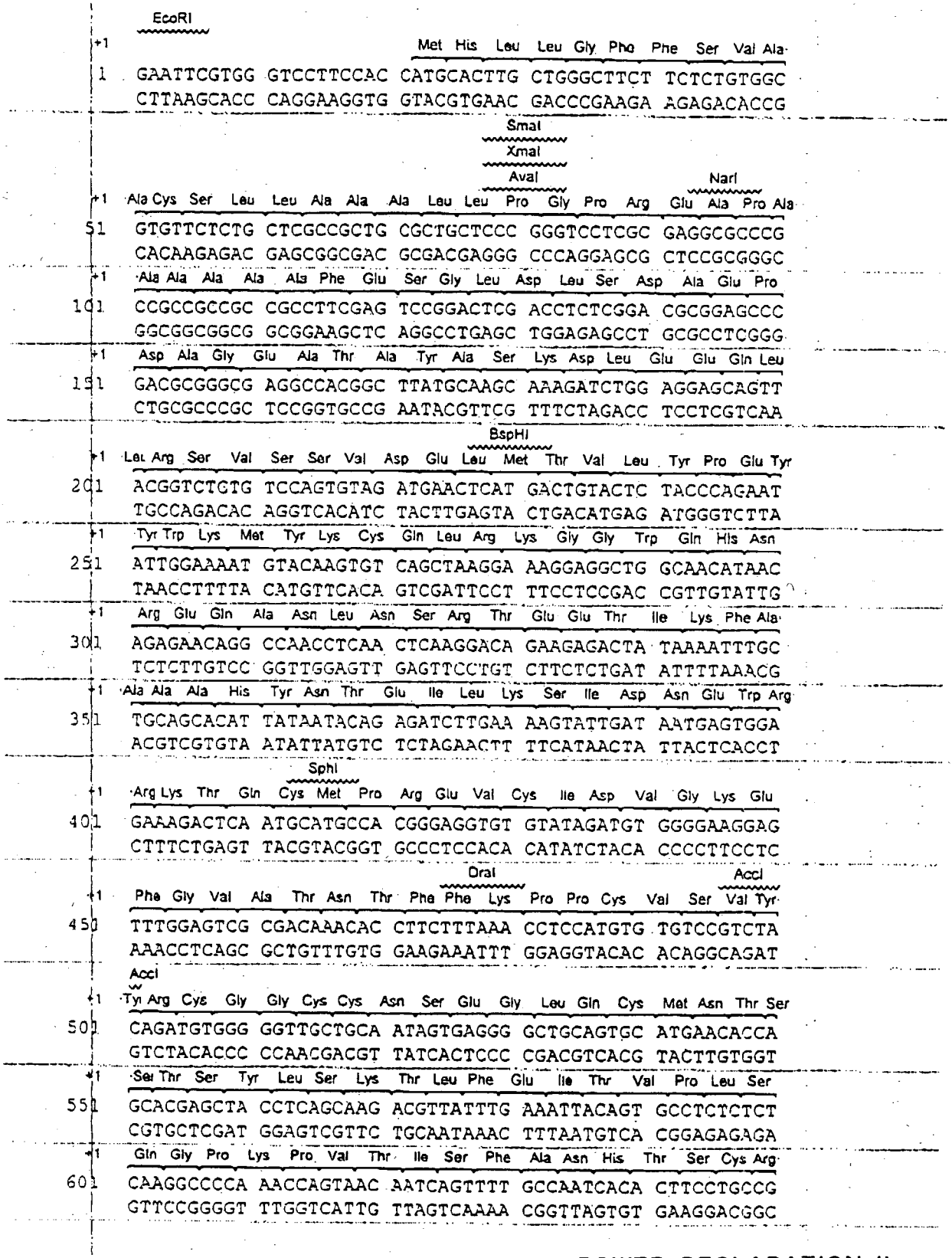


POWER DECLARATION II

APPENDIX II

VEGF 326+Signal





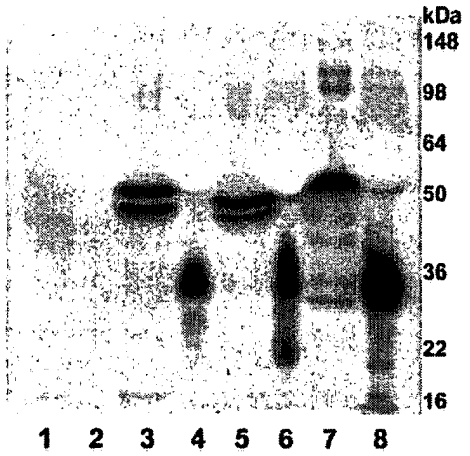
POWER DECLARATION II

APPENDIX III

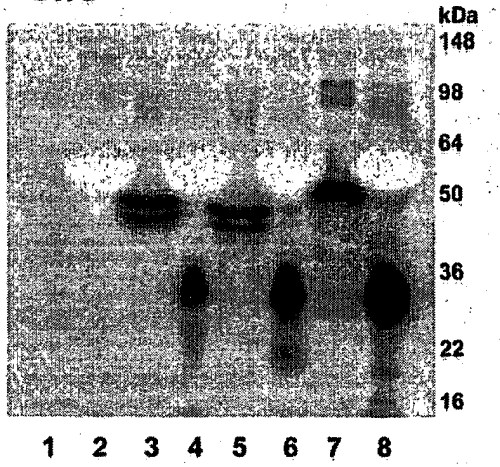
```
      +1  Arg Cys Met  Ser  Lys  Leu Asp  Val  Tyr Arg  Gln  Val His  Ser  Ile  Ile  Arg Arg
  651     ATGCATGTCT AAACTGGATG TTTACAGACA AGTTCATTCC ATTATTAGAC
          TACGTACAGA TTTGACCTAC AAATGTCTGT TCAAGTAAGG TAATAATCTG

      +1  Arg Ser Leu  Pro  Ala Thr  Leu  Pro Gln Cys  Gln  Ala Ala  Asn  Lys Thr Cys
  701     GTTCCCTGCC AGCAACACTA CCACAGTGTC AGGCAGCGAA CAAGACCTGC
          CAAGGGACGG TCGTTGTGAT GGTGTCACAG TCCGTCGCTT GTTCTGGACG

      +1  Pro Thr Asn  Tyr  Met Trp  Asn  Asn His  Ile  Cys Arg Cys  Leu  Ala Gln Glu
  751     CCCACCAATT ACATGTGGAA TAATCACATC TGCAGATGCC TGGCTCAGGA
          GGGTGGTTAA TGTACACCTT ATTAGTGTAG ACGTCTACGG ACCGAGTCCT

      +1  Glu Asp Phe  Met  Phe Ser  Ser  Asp Ala Gly  Asp  Asp Ser  Thr  Asp Gly Phe His
  801     AGATTTTATG TTTTCCTCGG ATGCTGGAGA TGACTCAACA GATGGATTCC
          TCTAAAATAC AAAAGGAGCC TACGACCTCT ACTGAGTTGT CTACCTAAGG

      +1  His Asp  Ile  Cys  Gly Pro  Asn  Lys Glu  Leu  Asp  Glu Glu  Thr  Cys Gln Cys
  851     ATGACATCTG TGGACCAAAC AAGGAGCTGG ATGAAGAGAC CTGTCAGTGT
          TACTGTAGAC ACCTGGTTTG TTCCTCGACC TACTTCTCTG GACAGTCACA

                BsrBI
      +1  Val Cys Arg  Ala  Gly Leu  Arg  Pro Ala  Ser  Cys Gly  Pro  His  Lys Glu Leu
  901     GTCTGCAGAG CGGGGCTTCG GCCTGCCAGC TGTGGACCCC ACAAAGAACT
          CAGACGTCTC GCCCCGAAGC CGGACGGTCG ACACCTGGGG TGTTTCTTGA

      +1  Leu Asp Arg  Asn  Ser Cys  Gln  Cys  Val Cys  Lys  Asn Lys  Leu  Phe Pro Ser Gln
  951     AGACAGAAAC TCATGCCAGT GTGTCTGTAA AAACAAACTC TTCCCCAGCC
          TCTGTCTTTG AGTACGGTCA CACAGACATT TTTGTTTGAG AAGGGGTCGG

      +1  Gln Cys Gly  Ala  Asn Arg  Glu  Phe Asp  Glu  Asn  Thr Cys  Gln  Cys Val Cys
 1001     AATGTGGGGC CAACCGAGAA TTTGATGAAA ACACATGCCA GTGTGTATGT
          TTACACCCCG GTTGGCTCTT AAACTACTTT TGTGTACGGT CACACATACA

      +1  Lys Arg Thr  Cys  Pro Arg  Asn  Gln Pro  Leu  Asn  Pro Gly  Lys  Cys Ala Cys
 1051     AAAAGAACCT GCCCCAGAAA TCAACCCCTA AATCCTGGAA AATGTGCCTG
          TTTTCTTGGA CGGGGTCTTT AGTTGGGGAT TTAGGACCTT TTACACGGAC

      +1  Cys Glu Cys  Thr  Glu Ser  Pro  Gln Lys  Cys  Leu  Leu Lys  Gly  Lys Lys Phe His
 1101     TGAATGTACA GAAAGTCCAC AGAAATGCTT GTTAAAAGGA AAGAAGTTCC
          ACTTACATGT CTTTCAGGTG TCTTTACGAA CAATTTTCCT TTCTTCAAGG

      +1  His His Gln  Thr  Cys Ser  Cys  Tyr Arg  Arg  Pro  Cys Thr  Asn  Arg Gln Lys
 1151     ACCACCAAAC ATGCAGCTGT TACAGACGGC CATGTACGAA CCGCCAGAAG
          TGGTGGTTTG TACGTCGACA ATGTCTGCCG GTACATGCTT GGCGGTCTTC

      +1  Ala Cys Glu  Pro  Gly Phe  Ser  Tyr Ser  Glu  Glu  Val Cys  Arg  Cys Val Pro
 1201     GCTTGTGAGC CAGGATTTTC ATATAGTGAA GAAGTGTGTC GTTGTGTCCC
          CGAACACTCG GTCCTAAAAG TATATCACTT CTTCACACAG CAACACAGGG

                                                        NotI
                                                        EagI
      +1  Pro Ser Tyr  Trp  Lys Arg  Pro  Gln  Met Ser  ***
 1251     TTCATATTGG AAAAGACCAC AAATGAGCTA AGCGGCCGCG
          AAGTATAACC TTTTCTGGTG TTTACTCGAT TCGCCGGCGC
```

Figure 1

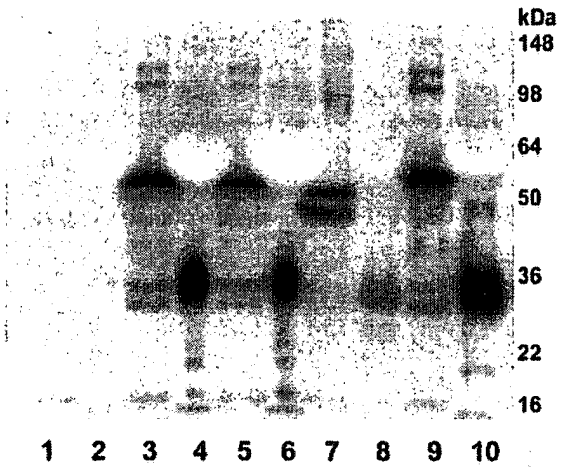
Gel 1



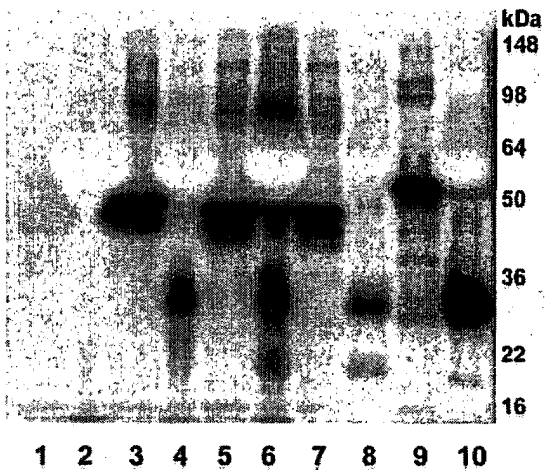
Gel 2



Gel 3



Gel 4



COMMONWEALTH OF AUSTRALIA

(Patents Act 1990)

IN THE MATTER OF: Australian Patent Application 696764 (73941/94). In the name of: Human Genome Sciences Inc.

- and -

IN THE MATTER OF: Opposition thereto by Ludwig Institute for Cancer Research, under Section 59 of the Patents Act.

STATUTORY DECLARATION

I, **Gary Baxter Cox** of Wray and Associates, 239 Adelaide Terrace, Perth WA 6101, Australia, declare as follows:

1. I am a Registered Patent Attorney, and a member of the firm Wray and Associates, Australian patent attorneys for Human Genome Sciences, Inc., the applicant in this matter. I have previously executed a statutory declaration in these proceedings on 13 December 2000 (my "first statutory declaration"), which contained 23 annexures. The annexures identified herein are numbered in consecutive order following the last annexure from my first statutory declaration.

2. Now produced and shown to me marked "**GBC-24**" is a copy of a statutory declaration by Peter Adrian Walton Rogers dated 26 October 2000 together with Exhibit 1 served in the opposition by Ludwig Institute for Cancer Research against Australian Patent Application 710696 by Genentech Inc.

WRAY & ASSOCIATES
Patent & Trade Mark Attorneys

6th Floor, GHD House
239 Adelaide Terrace, Perth
Western Australia 6000
Australia

Tel: (618) 9325 6122
Fax: (618) 9325 2883
Email: wray@wray.com.au
Our Ref: GBC: 100868

GBC

AND I make this solemn declaration by virtue of the Statutory Declarations Act, 1959 and subject to the penalties provided by that Act for the making of false statements in statutory declarations, conscientiously believing the statements contained in this declaration to be true in every particular.

DATED this: Twenty Second day of March 2002.

DECLARED at: Perth, Western Australia

BEFORE me:)

Gary Baxter Cox

Patent Attorney

COMMONWEALTH OF AUSTRALIA

(Patents Act 1990)

IN THE MATTER OF: Australian Patent Application 696764 (73941/94). In the name of: Human Genome Sciences Inc.

- and -

IN THE MATTER OF: Opposition thereto by Ludwig Institute for Cancer Research, under Section 59 of the Patents Act.

Annexure GBC-24

This is **Annexure GBC-24** referred to in my Statutory Declaration made this Twenty Second day of March 2002.

Gary Cox.

Gary Baxter Cox

WITNESS: M O'Sullivan

Commissioner for Declarations/Solicitor
Patent Attorney/Justice of the Peace

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No 710696 by Genentech, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

STATUTORY DECLARATION

I, Peter Adrian Walton Rogers of the Department of Obstetrics and Gynaecology, Monash University, Clayton, Victoria, Australia, do solemnly and sincerely declare as follows:

Introduction

1.1 I am presently working as Associate Professor and NH&MRC Principal Research Fellow with the Department of Obstetrics and Gynaecology, Monash University, Victoria, Australia. Since receiving my Ph.D in 1983, I have worked substantially continuously as a scientific researcher in the U.K. and in Australia in areas of cellular and molecular biology. My research has included substantial studies and explorations in fields of wound healing, microvasculature, vascular endothelial growth factors, growth of endothelial cells on vascular grafts, tumor angiogenesis and other areas related to angiogenesis. In addition to my own research efforts and my collaborations with others, I receive numerous invitations to speak at national and international symposiums in these fields of study, I supervise post-graduate research of others, and I have authored and co-authored numerous original research articles published in peer-reviewed journals. My detailed *curriculum vitae* is attached hereto as Exhibit 1.

1.2 I have been asked by the Ludwig Institute for Cancer Research ("Ludwig Institute") to serve as a scientific expert in connection with Ludwig Institute's opposition to the

issuance of a patent to Genentech, Inc., ("Genentech") based on Genentech's Australian Patent Application No. 710696 ("the Genentech application"). The patent application relates generally to a gene and protein for an alleged novel vascular endothelial growth factor (VEGF) called "VEGF-Related Protein" ("VRP"), and thus pertains to an area of biology closely related to my research and expertise. I understand that Ludwig Institute is a named co-applicant for a different patent application directed to subject matter that may be related to "VRP".

1.3 Ludwig Institute has explained to me that it has retained me for the purpose of providing expert scientific analysis of the Genentech application, as well as related literature, both past and contemporaneous, that may be relevant to the patentability of claims in the application. Ludwig Institute is compensating me for the time that I devote to providing my expert scientific analysis. However, I understand that I have an overriding duty to the Patent Office (and to any Australian Federal Court that should review the Patent Office decision) to provide objective scientific analysis that I believe to be truthful. I hereby affirm that, to the best of my knowledge and belief, factual statements herein are true and opinion statements herein represent my objective scientific opinion and analysis.

1.4 I believe that my background and experience, as outlined above, provides me with an understanding of the common general knowledge in the fields of the invention, in Australia, at the time that the U.S. priority application and the opposed Australian (PCT) application were filed. The relevant common general knowledge is the common general knowledge of an individual with an advanced degree (*e.g.*, Ph.D and/or M.D.), such as an individual being exemplified by biochemists, protein and/or polypeptide biochemists, molecular biologists, and/or cell biologists, or teams of biochemists, protein and/or polypeptide biochemists, molecular biologists, and/or cell biologists, involved in the isolation and characterization of nucleic acid sequences, automated or manual nucleic acid sequencing methods, performing and interpreting searches of publicly available databases for sequences displaying homology to a query sequence, transformation of prokaryotic and eukaryotic organisms with isolated nucleic acid sequences, expression of heterologous sequences in prokaryotic and

eukaryotic host cells and/or organisms, isolation and/or characterization of factors involved in cell growth and proliferation, especially but not limited to those factors associated with angiogenesis, in Australia at or before the priority date of the claims of the Genentech application.

1.5 Throughout this declaration, I may refer to Australian Patent Application No. 710696 using various terms such as "the opposed application," "the opposed patent," "the Genentech patent" or "the Genentech application." All such terms should be understood to refer to the same document. References to the "specification" should be understood as references to the descriptive portion of the application, including text and figures.

1.6 At the time that I execute this declaration in the year 2000, a significant body of literature has been published relating to the structure and functions of the gene and protein which the opposed patent refers to and I will refer to as "VRP." It is a complex protein that undergoes many stages of processing, and that appears to act as a growth factor for the vessels of the lymphatic system that convey lymph from tissues back into the blood. From my review of the file history of the Genentech application, I observed little or no mention or appreciation by the Australian Patent Office of any of the developments that occurred after Genentech filed its priority application. I think it would be helpful to the reader of this declaration to provide some context for the gene and protein of the invention that is not available from reading the Genentech application or its file history, but that may be relevant to the issues that I discuss below in this declaration in detail.

1.6.1 There is general agreement from at least three different research groups, including Genentech, that the human gene which encodes "VRP" encodes a polypeptide that is 419 amino acids in length. Other research groups that independently discovered the "VRP" gene accorded it different names, such as "VEGF-C" (see **Documents D1 & D2**) or "VEGF2" (for Vascular Endothelial Growth Factor 2, see **Documents D4 & D5**). Most of the investigative

reports that are published in respected scientific journals use these other names, especially "VEGF-C".

1.6.2 Reports in respected scientific periodicals indicate that the processing of "VRP" (VEGF-C) is not limited to the mere removal of a signal peptide. Rather, extensive proteolytic processing occurs at both the amino- and carboxyl-terminal ends of the 419 amino acid "prepro" polypeptide, resulting in a much smaller polypeptide (eg., only about 110-130 amino acids) that has enhanced and/or new biological activities relative to the larger pre-processed forms from which it was derived. (See **Documents D1**, **D15**, and **D16**, and paragraphs 3.6.3 and 3.7.4 below, and documents cited therein.) However, in the Genentech application filed in 1995, there is no evidence presented of complex proteolytic processing.

1.6.3 At least one significant study involving transgenic animals indicates that a prominent function of the protein product of the VRP gene *in vivo* is to modulate growth of the lymphatic endothelia. The study is reported in Document D16 at Example 29, and also was published in the prestigious scientific journal *Science*. (See Jeltsch et al., "Hyperplasia of lymphatic vessels in VEGF-C transgenic mice," *Science* (1997), 276 (5317):1423.) The researchers inserted a VEGF-C cDNA (which encodes a polypeptide at least 99.5% identical to VRP) construct into fertilised mouse oocytes to generate transgenic mice that express the construct. The cDNA was attached to a human K14 keratin promoter to cause increased expression of VEGF-C in the skin. The researchers found that skin from the transgenic mice (in comparison to normal mice) was atrophic and that connective tissue was replaced by large lacunae (spaces or cavities) devoid of red cells, but lined with a thin endothelial layer. These distended vessel-like structures resembled those seen in human lymphangiomas, which are tumors of the skin composed of masses of dilated lymph vessels. The endothelia surrounding these lacunae appeared to express Flt4 abundantly. Collectively, the data and other data collected by

the researchers suggest that the VEGF-C/VRP over-expression in the mice caused growth of vessels having features of lymphatic vessels.

Lack of Novelty of Claims of the Genentech Application

2.1. Introduction

2.1.1 Through my involvement in this matter, I understand that the claims of a patent define the scope of the invention protected by the patent, and that a patent may only claim novel subject matter. Patent claims that encompass subject matter that was described in other patents, publications, or other documents that existed at the time of the effective filing date of the patent claim are unacceptable under Australian patent law. Such documents that were published before the effective filing date constitute "prior art." It is my understanding that the effective filing date of a patent is the actual filing date, or sometimes the filing date of a priority application identified by the patent, if the priority application provides support for the claim. Claims that include prior art subject matter within their scope lack novelty, and are said to be "anticipated" by the prior art.

2.1.2 In this section of my declaration, I provide an analysis of whether claims in the Genentech application encompass within their scope subject matter that had been described in the literature prior to 08 September 1995, the priority date of the Genentech application.

2.1.3 I have reviewed the specification and claims of the Genentech application, the written prosecution history of the Genentech application in the Australian patent Office, and related prior art. To the extent that the scope of the claims can be determined at all,[1] I have determined that at least patent claims 1-4, 9-10, 12, 14-20, and 22-28 include within their scope subject matter that was described in the prior art before the earliest claimed priority date

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[1] As set forth below in the section titled "Lack of Clarity," many of the claims lack clarity. (See Section 5, below)

(08 September 1995). My detailed analysis follows. In paragraphs 2.2-2.2.2.1, I analyze the meaning of certain terminology that appears in many of the claims. Then, in paragraphs 2.3-2.17, I analyze the relationship of individual claims and prior art subject matter.

2.2 Analysis of the meaning and scope of limitations found in the claims.

2.2.1 Claim 1 of the Genentech application is directed to isolated biologically active human VEGF-related protein (VRP) having the ability to bind and stimulate phosphorylation of a Flt4 receptor. Almost all of the other claims (e.g., 2-20, 23-28) specify biologically active human VRP or refer back to an earlier claim that specifies biologically active human VRP.

2.2.1.1 The Genentech application explicitly defines "human VRP" at page 5, lines 12-25. The definition is noteworthy in that it explicitly includes a potentially infinite number of polypeptides,[2] and not just the polypeptide that the invention had reportedly isolated from humans and that has the amino acid sequence shown in Figure 1. For example, the definition at page 5 encompasses almost any biologically active deletional, insertional, or substitutional variants of the Figure 1 sequence that either (a) have at least 265 amino acids, or (b) include at least residues 1-29 of Figure 1. Thus, the definition of VRP is intended to include biologically active variants of the Figure 1 sequence that have been formed by removing or adding amino acids to the Figure 1 sequence, or by replacing amino acids in Figure 1 with alternative amino acids.

2.2.1.2 The Genentech application defines "biologically active" at page 5, beginning at line 26. The definition is "having the ability to bind to, and stimulate phosphorylation of, the Flt4 receptor." There is some ambiguity thereafter, because the next two sentences seem to contemplate stimulation/activation or

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[2] See also paragraphs 5.4-5.4.3 below, repeated here by reference.

inhibition of the receptor and receptor-mediated activities. Activation and inhibition are generally considered to be opposites. It is unclear whether the applicants intended this continued discussion to be part of the definition of "biologically active."

2.2.2. Claim 11 of the Genentech application recites, "The composition of claim 10 further comprising a cell growth factor other than said [human VRP] protein." Claim 13 contains a similar recitation.

2.2.2.1 The Genentech application does not appear to explicitly define the term "cell growth factor" as used in these claims. For example, there is no definition specifying that this term refers only to proteins that induce the growth of specific cell types and not others, such as the proteins recited at page 28, lines 9-12, of the Genentech application. The term, given its broadest reasonable interpretation, would appear to encompass any nutrient media, vitamin, mineral, salt, organic energy source, water, or other materials that living cells require to grow. Exemplary materials are discussed at page 19, lines 1-14, of the Genentech application, which pertain to mammalian cell growth media.

2.3. **Identification of Relevant Art.**

2.3.1 **Document D1** is a published Australian patent application which claims priority benefit from **Document D3**, which was filed on 01 August 1995 (as well as other applications filed in 1996). It was explained to me that, for novelty purposes, **Document D1** is prior to the Genentech application for subject matter that is disclosed in **Documents D1 and D3**, because the priority application **Document D3** was filed prior to the Genentech application priority date (08 September 1995). Thus, claims in the Genentech application that encompass subject matter that is disclosed in both **Documents D1 and D3** lack novelty over **D1 and D3**.

2.3.2 **Document D7** is a published Australian patent application that was filed as an international application on 09 June 1995, prior to the Genentech application priority date. Thus, for novelty purposes, **Document D7** is prior to the Genentech application

for everything that **Document D7** discloses. Claims of the Genentech application that encompass subject matter of **Document D7** lack novelty.

2.4. Analysis of individual claims.

2.4.1 In the following paragraphs, I analyze whether individual claims of the Genentech application encompass subject matter that was disclosed in the prior art (*e.g.*, the patent documents and journal articles that were published prior to 08 September 1995). The paragraphs below provide an analysis of claims with scope sufficiently large to encompass subject matter that had been disclosed in published literature prior to 08 September 1995, or disclosed in published Australian patent applications of others that claim priority filing dates prior to 08 September 1995. The publications to which I refer do not necessarily disclose the exact VRP nucleotide or deduced amino acid sequence shown in the Genentech application. However, as I explain herein, the claims at issue are not limited in scope to the exact VRP sequences disclosed in the application, but are much broader.

2.5 Claim 1

2.5.1 Claim 1 of the Genentech application is directed to "Isolated biologically active human VEGF-related protein (VRP) containing at least 265 amino acids having the ability to bind and stimulate phosphorylation of a Flt4 receptor."

2.5.2 As explained in paragraph 2.2.1.1, "Human VRP" is not limited to the single sequence shown in Figure 1, because it is defined as "a polypeptide sequence containing at least residues -20 to 399, inclusive, or residues +1 to 399, inclusive, of the amino acid sequence shown in Figure 1, including residues -5 to 399, inclusive, and residues -4 to 399, inclusive, of the amino acid sequence shown in Figure 1, as well as biologically active deletional, insertional, or substitutional variants of the above sequences having at least 265 amino acids and/or having at least residues +1 through 29, inclusive, of Figure 1." (See Genentech application at p. 5, lines 12-16.)

2.5.3 **Document D1** and its first priority application, **Document D3**, each disclose one or more purified and isolated human polypeptides of at least 265 amino acids and teach that the polypeptide(s) constitute a precursor of a Flt4 ligand (designated "VEGF-C") that binds Flt4 and stimulates Flt4 phosphorylation. (See, e.g., **Document D1** at pp. 7-9, 26-27, 49-50; Figure 8; and SEQ ID NO: 33; **Document D3** at p. 5; Figure 9; and SEQ ID NO: 33.) These polypeptide(s) is/are either identical to the 419 amino acid VRP sequence shown in Figure 1 of the Genentech application (or to a portion thereof of at least 265 amino acids), or is/are at least about 99% identical to the VRP sequence, with one or a few substitutional variations.[3] (See **Document D1** amino acid sequences at SEQ ID NO: 33 and Figure 8; **Document D3** at p. 9; Figure 9; and SEQ ID NO: 33.) Thus, **Documents D1 and D3** teach an isolated polypeptide that satisfies all of the limitations (structural and functional) of claim 1, and did so (through **Document D3**) prior to the priority date of the Genentech application.

2.6 Claims 2-4

2.6.1 Claims 2-4 of the Genentech application depend from claim 1 and further limit claim 1 only by specifying protein length in terms of amino acid ranges of 265-450 amino acids (claim 2); 300-450 amino acids (claim 3); and 350-450 amino acids (claim 4). These length limitations are met by the approximately

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3. The VRP sequence disclosed in the Genentech application contain an ambiguity in that the "TAT" at codon 94 of the cDNA depicted in Figure 1B encodes the amino acid tyrosine according to the universal genetic code, whereas Figure 1B teaches that the amino acid at position 94 of the amino acid sequence is a threonine. (Residue 94 of Figure 1 corresponds to residue 114 of the VEGF-C precursor sequence set for in SEQ ID NO: 33 of **Document D1**.) Throughout this section pertaining to novelty, I will frequently refer to the Flt4 ligand precursor polypeptide of **Documents D1 and D3**. It should be understood from paragraphs 2.5-2.5.3 that this polypeptide is sufficiently similar to the VRP sequence taught in the Genentech application to satisfy the definition of VRP taught in the Genentech application, since the definition permits substitutional variations.

350 amino acid VEGF-C sequence of **Document D1** and its first priority document. (See **Document D1** amino acid sequences at SEQ ID NO:33 and Fig. 8; **Document D3** at p. 9, Fig. 9, and SEQ ID NO:33.) Thus, the human VRP of claims 2-4 is not novel in view of the VEGF-C polypeptide and activity teachings in **Documents D1** and **D3**.

2.7 Claims 9-10

2.7.1 Claim 9 of the Genentech application recites, "A composition comprising the protein of any one of claims 1-8 and a pharmaceutically acceptable carrier." Claim 10 recites, "A pharmaceutical composition useful for promotion of vascular endothelial cell growth comprising a therapeutically effective amount of the protein of any one of claims 1-8 in a pharmaceutically acceptable carrier."

2.7.2 As explained in particulars 2.5-2.6.1, repeated here by reference, **Document D1** and its first priority application (**Document D3**) teach VEGF-C precursor polypeptides that meet the limitations of at least claims 1-4. Each of these documents also teach to mix VEGF-C polypeptides with an appropriate pharmaceutically acceptable vehicle and teach to use such polypeptides and compositions to, e.g., accelerate angiogenesis and to promote the endothelial functions of lymphatic vessels. (See, e.g., **Document D1** at pp. 15-17; **Document D3** at pp. 6-7 and claim 12.) Thus, **Documents D1 and D3** teach compositions that satisfy all of the structural and functional limitations of claims 9-10 of the Genentech application. **Documents D1/D3** contained these teachings before the priority date of the Genentech application.

2.7.3 The Genentech application is prophetic in the sense that it does not indicate (e.g., in working examples) that the inventors had actually prepared any pharmaceutical compositions embraced by claims 9-10. In this sense, the scientific evidence in **Documents D1** and **D3** relating to claims 9-10 meets or exceeds the supporting scientific disclosure for claims 9-10 found in the Genentech application.

2.8 Claim 12

2.8.1 Claim 12 of the Genentech application recites "Use of the protein of any one of claims 1-8 or the composition of claim 9 or 10 in the manufacture of a medicament for treating trauma affecting the vascular endothelium or for treating a dysfunctional state characterised by lack of activation or lack of inhibition of a receptor for VRP in a mammal."

2.8.2 As explained above in particulars paragraphs 2.5-2.7.3, repeated herein by reference, **Document D1** and its first priority application (**Document D3**) each teach VEGF-C precursor polypeptides which meet the limitations of at least claims 1-4, and teach to formulate the polypeptides with a pharmaceutically vehicle such as a diluent or carrier that satisfies the limitations of claims 9-10. These documents also teach that VEGF-C is a Flt4 ligand and contemplate use of the ligand to stimulate cells such as lymphatic endothelial cells that express the Flt4 receptor. (See, e.g., **Document D1** at pp. 16-17; **Document D3** at p. 6-7.) Use of VEGF-C to treat conditions such as wounds, regrowth of lymphatic vessels in transplants, to prevent inflammation, edema, or aplasia of lymphatic vessels, lymphatic obstructions, elephantiasis, and Milroy's disease is contemplated (see, e.g., **Document D1** at p. 15; **Document D3** at pp. 6-7). Thus, **Documents D1 and D3** teach the protein of claims 1-4, the composition of claims 9-10, and their use as recited in claim 12. **Documents D1/D3** contained these teachings before the priority date of the Genentech application.

2.8.3 The Genentech application does not indicate (e.g., in working examples) that the inventors had actually used the VRP protein of any of claims 1-8 or composition of claims 9-10 in the manufacture of a medicament as recited in claim 12. The Genentech application also fails to provide any scientific evidence that any particular dysfunctional state is characterized by lack of activation or lack of inhibition of a VRP receptor. Thus, the scientific evidence in **Documents D1 and D3** that supports claim 12 equals or exceeds

the supporting scientific evidence for claim 12 found in the Genentech application. In fact, the dysfunctional states relating to the lymphatic system described in **Documents D1 and D3** would appear to be among the more promising indications for VRP polypeptides based on initial *in vivo* activity studies that I have seen in the literature. (See paragraph 1.6.3, above.)

2.9 Claim 14

2.9.1 Claim 14 of the Genentech application recites "A method for stimulating the phosphorylation of a tyrosine kinase domain of a Flt4 receptor comprising contacting an extracellular domain of the Flt4 receptor with the protein of any one of claims 1-8."

2.9.2 As I explain in paragraphs 2.5-2.6.1, repeated here by reference, **Document D1** and its first priority application teach a Flt4 ligand precursor polypeptide that meets the limitations of at least claims 1-4. **Documents D1 and D3** also teach to use the Flt4 ligand to stimulate Flt4 phosphorylation by contacting the extracellular domain of Flt4 expressed in cells with the ligand. (See, e.g., **Document D1** at pp. 49-50; **Document D3** at pp. 25-26.) Thus, **Documents D1 and D3** teach the method recited in claim 14, and contained these teachings before the priority date of the Genentech application.

2.10 Claim 15

2.10.1 Claim 15 of the Genentech application recites, "A chimeric polypeptide comprising the protein of any one of claims 1-8 fused to a tag polypeptide sequence."

2.10.2 The Genentech application provides a definition of "epitope tagged" at page 6, first paragraph. Epitope tagging also is described at page 23. Since claim 15 recites "a chimeric polypeptide" and "a tag polypeptide" and does not recite "epitope tagged", I would conclude that this definition at page 6 provides guidance for interpreting claim 15, but does not necessarily totally restrict the definition of claim 15. For "epitope tagging" the tag polypeptide is said to

have enough residues to provide an epitope against which an antibody can be raised, and to be short enough such that it does not interfere with activity of VRP. Exemplary tag size ranges of 8-50 residues are taught. VRP fusions are also described at page 20 of the Genentech application.

2.10.3 **Document D1** and its first priority application, **Document D3**, explicitly contemplate expression of the Flt4 ligand protein as a chimeric/fusion protein. For example, these documents contemplate using a GST fusion protein to raise antibodies against the Flt4 ligand polypeptide. (See **Document D1** at p. 51, lines 29-31; **Document D3** at p. 27, lines 12-13.) In my opinion GST sequences fused to a polypeptide of interest could be used as tag sequences to isolate the polypeptide of interest. (Antibodies could be raised against the GST sequences which would not substantially cross-react with other epitopes.) Thus, I would conclude that **Documents D1** and **D3** describe a Flt4 ligand/GST chimeric polypeptide that satisfies the limitations of claim 15, thereby anticipating claim 15.

2.11 Claims 16 and 17

2.11.1 Claim 16 of the Genentech application recites "A monoclonal antibody which binds to the protein of any one of claims 1-8 and neutralises a biological activity of the protein."

2.11.2 As explained in detail in paragraphs 2.5-2.6.1, repeated here by reference, **Document D1** and its first priority application (**Document D3**) each teach Flt4 ligand precursor polypeptides which meet the limitations of at least claims 1-4. These documents also teach that antibodies, both monoclonal and polyclonal, can be generated against the Flt4 ligand polypeptides. (See, e.g., **Document D1** at p. 14, 51; **Document D3** at p. 6, 27.) These documents teach that antibodies are potential Flt4 ligand antagonists to, *e.g.*, control endothelial cell proliferation and block ligand-mediated stimulation of the Flt4 receptor. (See, e.g., **Document D1** at pp. 14, 16; **Document D3** at pp. 7, 8.) Thus, prior to the filing date of the Genentech application, **Documents D1/D3**

taught to make monoclonal antibodies recited in claim 16 and taught that such antibodies could be used to neutralize the receptor-stimulating biological activity of the Flt4 ligand protein.

2.11.3 Claim 17 depends from claim 16 and recites that the biological activity of the protein is promoting neovascularization or vascular permeability or vascular endothelial cell growth in a mammal.

2.11.4 The limitations of claim 17 are met by **Documents D1** and its first priority application **Document D3**, for the reasons discussed with respect to claims 12 and 16 in paragraphs 2.8-2.8.3 and 2.11.1-2.11.2, repeated here by reference. Promoting regrowth or permeability of lymphatic vessels is explicitly taught in **Documents D1 and D3** as activities/uses of the Flt4 ligand. (See **Document D1** at p. 15; **Document D3** at pp. 6-7, for example.) Thus, claim 17 is not novel in view of **Documents D1 and D3**.

2.12 Claim 18

2.12.1 Claim 18 specifies a monoclonal antibody that binds to the N-terminal portion from residues -20 through 137, inclusive, or from residues 1 through 137, inclusive, of the amino acids sequence shown in Figure 1.

2.12.2 Nothing in the Genentech application indicates that these regions of VRP correspond to an important functional domain of VRP, or have special significance for anti-VRP antibody production (e.g., because they produce antibodies more useful than antibodies raised against other portions of VRP). Rather, residues -20 to 137 seem to have been chosen only because they do not correspond to portions of VRP that are encoded by sequences that existed in databases prior to the filing date of the Genentech application. (See Figure 4.)

2.12.3 A mature (processed) form of VEGF-C taught in **Documents D1** and **D3** includes residues corresponding to residues 83-137 of the sequence shown in

Figure 1 of the Genentech application. (See N-terminal sequence analysis in **Document D1**, p. 43; see also **Document D3** at p. 19, lines 9-19.) In fact, **Documents D1** and **D3** explicitly contemplate making (or have made) antibodies to the amino terminal peptide portion of mature VEGF-C, which corresponds to a peptide beginning at about residue 83 of the VRP sequence taught in Figure 1 of the Genentech application and referred to in claim 18. (See **Document D1** at p. 51, lines 27-31, and page 64, lines 1-30; **Document D3** at p. 19, lines 9-19, and p. 27, lines 10-11.) For example, an amino terminal peptide of 18 or 23 residues of mature VEGF-C isolated from PC-3 cells, as taught in **Documents D1/D3**, corresponds with approximately amino acids 83-100 or 83-105 of the VRP sequence taught in Figure 1 of the Genentech application. Thus, polyclonal or monoclonal antibodies raised against the amino terminal VEGF-C peptide, as taught in **Documents D1/D3**, are antibodies that bind to the N-terminal portion of VRP from -20 through 137 of the amino acid sequence of Figure 1 as recited in claim 1 of the Genentech application, because the larger sequence from -20 to 137 recited in claim 18 includes the smaller sequence from 83-105 taught in **Documents D1/D3** for use as an antigen. Thus, the antibodies taught in **Document D1** and its first priority application (**Document D3**), discussed with respect to claim 16 in paragraphs 2.10-2.10.2, are encompassed by claim 18.

2.13 Claims 19 and 20

2.13.1 Claim 19 of the Genentech application recites, "A composition comprising the antibody of one of claims 16, 17 or 18 and a pharmaceutically acceptable carrier."

2.13.2 **Document D1** and its priority application (**Document D3**) explicitly and/or inherently teach a composition comprising all of the limitations of claim 19. For example, **Documents D1** and **D3** teach the antibodies of claims 16-18, as described in detail in paragraphs 2.11 - 2.12.3, repeated here by reference. With respect to the Flt4 ligand, the documents explicitly teach to make pharmaceutical compositions using pharmaceutically acceptable carriers,

which is the conventional approach for any substance that is to be administered therapeutically. (See, e.g., **Document D1** at p. 15; **Document D3** at p. 6, claim 12.) Both **Documents D1** and **D3** contemplate therapeutic and diagnostic uses of anti-Flt4 ligand antibodies *in vivo* (see, e.g., **Document D1** at p. 14, 16; **Document D3** at pp. 6-7), and any practitioner in the art would know that such antibodies (like the ligand) would only be administered to a patient diluted in a pharmaceutically acceptable carrier. Thus, it is my opinion that the teachings relating to antibodies and therapy in **Documents D1** and **D3** expressly or inherently satisfy the limitations of claim 19.

2.13.3 Claim 20 of the Genentech application recites, "Use of the antibody of any one of claims 16-18 or the composition of claim 19 in the manufacture of a medicament for treating diseases or disorders characterised by undesirable excessive neovascularization or vascular permeability in a mammal or for treating a dysfunctional state characterized by excessive activation or inhibition of a receptor for VRP in a mammal."

2.13.4 All of the limitations of claim 20 are met by **Document D1**, as discussed above, e.g., with respect to claims 16-18 and 9-10, which the Opponent hereby repeat by reference. (See paragraphs 2.7-2.7.3 and 2.11-2.12.2.)

2.13.5 The Genentech application does not indicate (e.g., in working examples) that the inventors had actually prepared any antibodies embraced by claims 16-18, or prepared compositions embraced by claim 19; or used such antibodies or compositions in the manufacture of a medicament as recited in claim 20. Thus, the scientific data in support of these claims in **Documents D1** and **D3** meets or exceeds the supporting scientific data for claims 16-20 found in the Genentech application.

2.14 Claim 22

2.14.1 Claim 22 of the Genentech application recites, "A method for treating Karposi's [sic] sarcoma or a dysfunctional state characterised by excessive activation of inhibition of a receptor for VRP in a mammal comprising administering to the mammal an effective amount of a VRP antagonist."

2.14.2 **Document D1** and its first priority application (**Document D3**) teach an Flt4 ligand precursor that satisfies the definition of "VRP" and teach that the Flt4 ligand binds and stimulates the Flt4 receptor. (See, e.g., **Document D1** at pp. 7-9, 26-27, 49-50; **Document D3** at pp. 5, 25-26. See also paragraphs 2.5-2.6.1, repeated here by reference.) Likewise, these documents teach to use (e.g., administer) inhibitors of the Flt4 ligand to treat dysfunctional states characterized by excessive activation of the Flt4 receptor. (See, e.g., **Document D1** at pp. 15-16; **Document D3** at pp. 6-7.) Thus, the teachings of **Document D1** and its first priority application meet the limitations of claim 22.

2.14.3 **Documents D7-D8** disclose, for example, the Flt4 receptor tyrosine kinase; antibodies that specifically recognize the extracellular domain of Flt4 receptor; and methods of stimulating or antagonizing the function of Flt4 in lymphatic vascularization and in inflammatory, infectious and immunological conditions using pharmaceutical compositions comprising Flt4 binding compounds, such as Flt4 antibodies. **Document D7-D8** contemplate treatment of conditions where Flt4 function is associated with disease such as metastatic cancers, lymphomas, inflammation, infections, and immunological diseases. (See, e.g., **Documents D7-8** at pp. 3-5 (especially p. 5, lines 24-32) and Example 9.) The Genentech application teaches that the Flt4 receptor is a receptor for VRP. Thus, anti-Flt4 antibodies that block Flt4 stimulation constitute VRP antagonists, because such antibodies antagonize (inhibit) VRP-mediated stimulation of Flt4. Thus, use of materials and methods as taught in **Documents D7 and D8** for administering anti-Flt4 antibodies to mammals for

these stated purposes meet the limitations of claim 22 of the Genentech application.

2.14.4 The Genentech application is prophetic in that it does not indicate (e.g., in working examples or scientific data) that the inventors had actually used a VRP antagonist to treat Kaposi's sarcoma or any dysfunctional state as recited in claim 22. Thus, the scientific data in **Documents D1-D3** and **D7-D8** that is relevant to claim 22 meet or exceed the supporting data for claim 22 found in the Genentech application.

2.15 Claim 23

2.15.1 Claim 23 of the Genentech application recites, "An isolated mucleic [sic] acid molecule encoding the protein of any one of claims 1-8."

2.15.2 As explained in paragraphs 2.5-2.6.2, repeated here by reference, **Document D1** and its first priority application (**Document D3**) each teach Flt4 ligand polypeptides and/or polypeptide precursors that meet all of the limitations of at least claims 1-4. Each of these documents also teach polynucleotides encoding the polypeptides. (See, e.g., **Document D1** nucleotide sequences at SEQ ID NO: 32; **Document D3** nucleotide sequences at SEQ ID NO: 32 and Figure 9.) Thus, **Document D1** and priority document teach nucleic acids that satisfy all of the limitations of claim 23.

2.16 Claims 24-26

2.16.1 Claim 24 of the Genentech application recites, "The nucleic acid molecule of claim 23 further comprising a promoter operably linked to the nucleic acid molecule." Claim 25 recites, "A vector comprising the nucleic acid molecule of claim 23." Claim 26 recites, "An expression vector comprising the nucleic acid molecule of claim 23 operably linked to control sequences recognised by a host cell transformed with the vector."

2.16.2 As explained in paragraphs 2.15-2.15.2 and 2.5-2.6.2, repeated here by reference, **Documents D1 and D3** teach nucleic acid molecules that satisfy the requirements of claim 23. **Document D1** and its first priority application (**Document D3**) also teach and claim vectors comprising a DNA encoding the Flt4 ligand, and host cells comprising the vectors. Vectors capable of expressing the Flt4 ligand under the control of appropriate promoters and other control sequences are explicitly contemplated. (See, e.g., **Document D1** at p. 13 & claims 27-28; **Document D3** at p. 6 and claims 5-7.) Thus, **Document D1** and its first priority application, **Document D3**, teach the additional limitations of claims 24-26.

2.17 Claims 27-28

2.17.1 Claim 27 of the Genentech application recites, "A host cell comprising the nucleic acid molecule of claim 23."

2.17.2 The teachings of **Documents D1** and its first priority application (**Document D3**) meet the limitations of claims 23-26 for the reasons discussed in paragraphs 2.15-2.16.2, repeated here by reference. In addition, **Documents D1** and **D3** teach host cells that comprise vectors that comprise the nucleic acids that satisfy the limitations of claim 23. (See, e.g., **Document D1** at p. 13, lines 15-27, pp. 49-50 (Example 11), p. 54 (Example 13), and so on; **Document D3** at p. 5, lines 26-27, p. 6, lines 2-7, pp. 25-26 (Example 11), and claim 7.) Thus, the teachings of **Documents D1** and **D3** satisfy all of the limitations of claim 27 of the Genentech application.

2.17.3 In addition, **Documents D1** and **D3** each teach the prostatic adenocarcinoma cell line PC-3 which produces an Flt4 ligand polypeptide that is identical or essentially identical to the VRP sequence taught in the Genentech application, and that satisfies the limitations of claim 1 of the Genentech application. (See Examples 4-5 of **Documents D1** and **D3**. The cell line secretes a proteolytically processed form of the polypeptide.) This cell line inherently comprises a nucleic acid molecule that encodes the Flt4 ligand protein that it

produces. This fact would be generally accepted by competent practitioners in this field, since the process by which cells make proteins involves transcribing and translating a nucleic acid molecule in the cells that encode the protein. Moreover, the fact that the PC-3 cell line comprises a nucleic acid that encodes the Flt4 ligand protein is confirmed by the cDNA isolation experiments described in Examples 6-10 of **Documents D1** and **D3**. (The ability to isolate the Flt4 ligand cDNA means that the cells comprise DNA and RNA nucleic acid molecules that encode the Flt4 ligand.) Thus, unless there is a requirement for claim 27 that the VRP nucleic acid of the cell must have first been physically isolated and then introduced into the cell, it would appear that the PC-3 cell line described in **Documents D1** and **D3** and deposited with the ATCC also satisfies the requirements of claim 27. (Human cells in nature also would satisfy the limitations of claim 27 under this analysis.)

2.17.4 Claim 28 recites, "A method of producing VRP comprising culturing the host cell of claim 27 and recovering VRP from the host cell culture."

2.17.5 **Document D1** and its first priority application (**Document D3**) each provide and claim vectors comprising a nucleic acid molecule encoding the Flt4 ligand, and host cells comprising the nucleic acids or vectors, as explained in detail above with respect to claims 23-27 in paragraphs 2.15-2.17.3, repeated here by reference. Vectors capable of expressing the Flt4 ligand under the control of appropriate promoters and other control sequences are explicitly contemplated. Purification of the Flt4 ligand from culture medium, e.g., via Flt4 affinity chromatography, also is taught. (See, e.g., **Document D1** at pp. 13, 41-43; **Document D3** at pp. 6, 17-19.) Thus, **Documents D1** and **D3** teach a method that meets the limitations of claim 28.

D. Conclusion

2.18For the reasons outlined above, it is my opinion that at least claims 1-4, 9-10, 12, 14-20, and 22-28 are anticipated by the prior art.

Insufficiency

A. Introduction

3.1 Through my involvement in this matter, it is my understanding that Australian patent law (Section 40(2)(a)) includes a sufficiency requirement that focuses on whether the specification of a patent application is sufficient to disclose the method of carrying out the invention to a person reasonably competent in the relevant field of endeavor and equipped with the common general knowledge in that field.

3.1.1 It was explained to me that the evaluation for sufficiency should take into account the common general knowledge in the art, in the sense that gaps in a patent application are not necessarily problematic when the skilled practitioner can fill the gaps with reference to the common general knowledge. At the same time, for sufficiency to exist, further inventive ingenuity should not be required to practice the claimed invention. If a competent person cannot achieve the promised result because of deficiencies in the information given in the specification, there is insufficiency.

3.1.2 I was asked to consider whether the specification of the Genentech application included teachings that were commensurate in scope with the claims. It was explained to me that the directions provided in the specification must be sufficient for the execution of the invention throughout the breadth or range of the claims, and that an applicant who chooses to claim an invention broadly has an obligation to make a correspondingly wide disclosure.

3.1.3 It was also explained to me that the sufficiency of an application's disclosure is evaluated as of the application's filing date and/or priority date, and not from the state of the art as it exists today. If the claimed subject matter is insufficiently supported by the priority application (*e.g.*, the priority application is non-enabling), then the claims are not entitled to the benefit of the priority date.

3.1.4 In this section of my declaration, I provide an analysis of whether the specification of the Genentech application contains a disclosure sufficient to practice the claimed invention.

B. Analysis

3.2 Inadequate support for VRP up to 450 amino acids in length.

3.2.1 Claims 1-4, 9-17, 19-20, and 23-28 recite a VEGF related protein (VRP) containing at least up to about 450 amino acids. In particular, dependent claims 2-4 explicitly recite VRP size ranges up to 450 amino acids. Independent claim 1 is apparently intended to be at least as broad as the claims which depend from it, so by implication claim 1 is apparently intended to cover VRP of at least about 450 amino acids. Claims 9-17, 19-20, and 23-28 depend from claims 1-4 without further restricting the maximum size (amino acid seqence length) of VRP.

3.2.2. However, the Genentech application does not describe any VRP sequence longer than 419 amino acids. (See, e.g., Genentech application at Figure 1.) Thus, I would conclude that the teachings of VRP proteins in the Genentech application are not commensurate in scope with the claims, from the standpoint of the claim limitations directed to VRP protein length (e.g., of about 450 amino acids).

3.3 Inadequate explanation of VRP opposing activities

3.3.1. Claims 12-13, 20, and 22 recite two diametrically opposed activities for VRP (claims 12-13) or for VRP antagonists (claims 20, 22).

3.3.2 For example, claim 12 contemplates using a biologically active VRP protein to treat EITHER a dysfuctional state characterized by lack of activation of a VRP receptor OR a dysfuctional state characterized by lack of inhibition of a VRP receptor. Since the Genentech application defines VRP biological activity as a receptor stimulating activity (see p. 5, line 26 et seq.), it would seem plausible that VRP might be used to treat a disease that is characterized by lack of activation of the VRP receptor. (The

Genentech application does not actually demonstrate such disease treatment.) However, there is no clear scientific rationale why a biologically active VRP would be useful to remedy a disease characterized by *lack of inhibition* of a VRP receptor, because a biologically active VRP would not be expected to inhibit a VRP receptor, but rather would be expected to activate it. (Further activation of a VRP receptor in a patient having a disease characterized by lack of inhibition of VRP receptors would be expected to exacerbate, rather than alleviate, the disease or its symptoms.) Likewise, there is no explanation of how a single molecule (e.g., a biologically active VRP molecule) possesses two opposed activities. There also is no explanation in the Genentech application as to when the VRP molecule possesses one activity versus the other, or how to select a particular activity for practicing the recited method.

3.3.3. Analogous reasoning applies to claim 20 of the Genentech application, which recites use of an antibody which binds and "neutralises" biologically active VRP to treat a dysfunctional state characterized by *either excessive activation or inhibition* of a VRP receptor. The Genentech application fails to explain, scientifically, how an antibody that neutralizes VRP biological activity could treat both diseases characterized by excessive receptor activation or excessive receptor inhibition. (Neutralizing VRP protein in a patient having a disease characterized by excessive inhibition of a VRP receptor would be expected to further inhibit activity of the receptor, thereby exacerbating the disease or its symptoms.)

3.3.4. The reasoning of paragraph 3.3.2 applies equally to claim 13, which depends from claim 12.

3.3.5. Similarly, claim 22 recites a method for treating a dysfunctional state characterized by *either excessive activation or inhibition* of a VRP receptor with a VRP antagonist. The Genentech application identifies VRP antibodies as VRP antagonists, and the reasoning of paragraph 3.3.3 applies to claim 22. Scientifically, it is unclear how an antagonist of a VRP receptor would be expected to be useful to treat a disease state that is characterized by excessive inhibition of the VRP receptor. An antagonist might be expected to worsen such a dysfunctional state.

3.3.6 In addition to failing to adequately explain the inconsistent VRP activities recited in claims 12-13, 20, and 22, the Genentech application fails to adequately explain what dysfunctional states are encompassed by claims 12-13, 20, and 22.

3.3.6.1 In its definitions section, the Genentech application identifies a huge number of diseases or disorders allegedly characterized by undesirable excessive neovascularization or vascular permeability (see, e.g., page 8) but no specific dysfunctional states characterized by excessive activation or inhibition of the VRP receptor, Flt4. Then at pages 24-25, the application continues to discuss a large number of therapeutic uses associated with blood vessel regrowth or repair. At pages 34-35, the application presents a large number of therapeutic uses associated with VRP antibodies, including treatment of about forty neoplastic disorders. However, there is an inadequate explanation of which of the many target diseases and conditions constitute the "dysfunctional state" recited in the claims.

3.3.7 Even if I ignore the internal inconsistency of claims 12-13, 20, and 22, and the inadequate explanation of what dysfunctional states are intended, I reach the conclusion that the Genentech application provides inadequate explanation for how to treat the disorders or why the treatment would even be expected to work.

3.3.7.1 The Genentech application teaches, through its citation of prior art, that Flt4 expression during development is first observed in mouse embryos in endothelial cell precursors, and then, as development proceeds, becomes confined to the venous and lymphatic endothelium and finally becomes restricted to the lymphatic vessels. (See pp. 1-2.) The application further teaches, "Consistent with this finding, adult human tissues show Flt4 expression in lymphatic endothelia while there is a lack of expression in arteries, veins, and capillaries." (See p. 2, first paragraph.)

3.3.7.2 The receptor identified for VRP is Flt4, and VRP biological activity is defined as the ability to bind to and stimulate phosphorylation of Flt4. (See Genentech application at p. 5.) The Genentech application teaches that VRP does not interact appreciably with the VEGF receptors Flt1 and Flk1 that are known to be expressed in the endothelia of blood vessels. (See Genentech application at p. 3, first paragraph, and p.43, last paragraph.)

3.3.7.3 The Genentech application does not demonstrate that VRP or VRP antibodies are effective to treat any of the conditions discussed in the application.

3.3.7.4 In view of the analysis in the preceding paragraphs 3.3.6-3.3.7.3, it is my opinion that the Genentech application contains an inadequate explanation for the uses enumerated generically in claims 12-13, 20, and 22 and specifically throughout the application's discussion of therapy. A competent practitioner in this field would discern from the application that VRP stimulates Flt4 receptor, whose expression is restricted to lymphatic endothelia, and does not appreciably interact with known blood vessel receptors Flt1 and Flk1. The teaching that VRP interacts only with a receptor that is not expressed appreciably in blood vessels would be inadequate for understanding how to treat the many disorders related to blood vessels recited in the claims and application, or the other disorders recited in the application. Since there are no examples of treatment and no explanation or rationale as to why the treatment would work, it is my opinion that the Genentech application provides inadequate support for the uses or claims 12-13, 20, and 22.

3.4 Inadequate teachings relating to Kaposi's sarcoma.

3.4.1 Claim 22 recites a method for treatment of Kaposi's sarcoma. Kaposi's sarcoma is a serious cancer, and the Genentech application fails to demonstrate successful treatment of this sarcoma. Likewise, the Genentech application fails to teach successful treatment in an animal model that is considered predictive of success in humans, and fails to teach the killing of such sarcoma cell *in vitro*. In fact, even though the Genentech application suggests that VRP antibodies could be used to treat

roughly forty neoplastic conditions (see pp. 34-35), the Genentech application does not provide any scientific evidence or even scientific reasoning as to why treatment of Kaposi's sarcoma (not to mention the approximately forty other unclaimed diseases) would be effective.

3.5 Inadequate characterization of the complete polypeptide genus encompassed by claims.

3.5.1. The support for the claims (e.g., at least claims 1-4, 9-17, 19-20, 22-28) provided by the Genentech application is inadequate because the characterizing features of the claims could be construed to cover products (e.g., polypeptides, polynucleotides, antibodies, antagonists) and uses of such products that were not known to exist and that a person reasonably competent in the field would not have known existed; and that owe nothing to the teachings of the Genentech application.

3.5.2 Claim 1 recites, "Isolated biologically active human VEGF-related protein (VRP) containing at least 265 amino acids having the ability to bind and stimulate phosphorylation of a Flt4 receptor." The dependent claims identified above contain no further limitation specifically directed to *a particular* amino acid sequence, such as the Figure 1 VRP cDNA and amino acid sequences depicted in the Genentech application.

3.5.3 The stated definition of "human VRP" in the Genentech application explicitly includes deletional, insertional, and substitutional variants of the single VRP sequence taught in Figure 1 of the application. (See analysis in paragraph 2.2.1.1 above, repeated here by reference.)

3.5.4 Subsequent to the filing of the Genentech application, researchers who are not the inventors of the Genentech application have discovered at least one other human growth factor, VEGF-D, that binds and stimulates phosphorylation of a Flt4 receptor. VEGF-D is characterized in the following scientific and patent literature:

3.5.4.1 **Document D12:** Achen, *et al.*, "Vascular endothelial growth factor D (VEGF-D) is a ligand for the tyrosine kinase VEGF receptor 2 (Flt1) and VEGF receptor 3," *Proc. Natl. Acad. Sci. (USA), 95(2)*: 548-553 (1998).

3.5.4.2 **Document D13:** Genbank Accession No. AJ000185, "Vascular endothelial growth factor-D."

3.5.4.3 **Document D14:** International Patent Application No. PCT/US97/14696, filed 21 August 1997 by Ludwig Institute for Cancer Research et al. (WO 98/07832).

3.5.5 These documents disclose Vascular Endothelial Growth Factor-D (VEGF-D) polynucleotides and polypeptides. VEGF-D is a polypeptide whose properties include the ability to bind and stimulate phosphorylation of Flt4 receptor, the stated biological activity of VRP polypeptides in the Genentech application. VEGF-D is encoded by a completely different gene than the gene that encodes VRP, and the VEGF-D gene and protein were not known to exist, and could not have been known to exist, from the Genentech application.

3.5.6 VEGF-D is not VRP: VEGF-D is a different size protein than VRP (354 vs. 419 amino acids) and is encoded by a different human gene. In fact, an alignment of the human VRP and VEGF-D sequences indicated that the molecules share only about 48% amino acid identity, meaning more mismatches than matches. (See **Document D12** at p. 550.) Even though VEGF-D owes nothing to the teachings of the Genentech application, Genentech may assert that VEGF-D protein and cDNA satisfy claim 1 and dependent claims on the basis that VEGF-D "matches" the sequence of Figure 1 of the Genentech application, except for insertional, substitutional, and deletional variations. The claims would be asserted to encompass VEGF-D on the theory that insertional, substitutional, and deletional changes to the VRP sequence taught in the Genentech application are all purportedly within the definition of "human VRP" in the application.

3.6 Inadequate explanation of VRP activity and polypeptides which possess VRP activity.

3.6.1 The Genentech application provides inadequate support for at least claims 6-7, 9-14, 19, and 23-28, in that these claims purport to define a genus of biologically active VRP proteins (or polynucleotides encoding the biologically active VRP, vectors, or host cells) with reference to particular amino acid subsequences (*e.g.*, Figure 1, residues 1-29 or 1-137 or -20 to 29 or -20 to 137) that are insufficient to confer VRP biological activity.

3.6.2 The Genentech application defines VRP biological activity as the ability to bind and stimulate phosphorylation of a Flt4 receptor. (See analysis in paragraphs 2.2.1.2 and 5.9-5.9.3, repeated by reference.)

3.6.3 Significant scientific and patent literature have been published in which scientists have examined the portion of the VRP sequence that is required for binding and stimulating phosphorylation of VRP. (See, e.g., **Document D15:** Joukov *et al.*, "Proteolytic Processing regulates receptor specificity and activity of VEGF-C," *EMBO J., 16(13)*: 3898-3911 (1997); and **Document D16:** International Patent Application No. PCT/US98/01973, filed on 2 February 1998 by Ludwig Institute for Cancer Research et al. (WO 98/33917)). These documents provide scientific evidence that a fragment of VRP lacking at least amino acids -20 to 93 of the VRP sequence of the Genentech application (Figure 1) can bind and stimulate Flt4, suggesting that these amino acids are unnecessary for Flt4-binding and Flt4-phosphorylation activity. The documents provide evidence that the residues necessary for Flt4 binding and phosphorylation are found within approximately amino acids 93-193 of the VRP sequence. The evidence developed through experimental research by non-Genentech scientists indicates that VRP residues 1-29 or 1-137 or -20 to 29 or -20 to 137, recited in the claims for defining biologically active human VRP, are neither necessary nor sufficient (as a group) to confer the stated activity.

3.6.4 The Genentech application provides no evidence of its own that residues 1-29 or 1-137 or -20 to 29 or -20 to 137 confer Flt4-binding or Flt4-phosphorylation activity. These recited residues were apparently selected not because the inventors had

stimulate Flk1. (See, e.g., **Document D15:** Joukov *et al.*, "Proteolytic Processing regulates receptor specificity and activity of VEGF-C," *EMBO J., 16(13)*: 3898-3911 (1997); and **Document D16:** International Patent Application No. PCT/US98/01973, filed on 2 February 1998 by Ludwig Institute for Cancer Research et al. (WO 98/33917)). This discovery that Flk-1 can act as a second receptor (for VRP fragments) is directly contrary to the teachings in the Genentech application, even though fragments of the VRP sequence taught in the Genentech application are apparently intended to constitute VRP (according to the definition of "VRP" in the application).

3.7.5 Thus, the claims that recite the genus of VRP receptors find inadequate support in the application, which fails to identify at least one receptor for a VRP fragment.

C. **Conclusion**

3.8 Based on the foregoing analysis, I would conclude that at least claims 1-4, 6-7, 9-17, 19-20, and 22-28 lack adquate support in the Genentech application.

Claims Not Fairly Based

A. **Introduction**

4.1 Through my involvement in this matter, it is my understanding that Australian patent law includes a "fair basis" requirement that focuses on whether an invention as claimed is commensurate with the disclosure in an application. It was explained to me that a claim whose scope goes beyond the disclosure of the description found in the specification (*i.e.*, a claim to an invention for which there is no real and reasonably clear disclosure) is not fairly based, and should not be granted. I was told that "fair basis" is a fact-specific inquiry that must be made on a case-by-case basis and with consideration of the common general knowledge in the field(s) of the invention. However, I was told that certain guiding principles/inquiries are relevant to any fair basis analysis:

4.1.1 For example, one line of inquiry focuses on whether or not the alleged invention as claimed is broadly described in the specification.

4.1.2. Another inquiry is whether or not there is anything in the specification which is inconsistent with the alleged invention as claimed.

4.1.3 Another inquiry is whether or not the claim includes as a characteristic of the invention a feature as to which the specification is wholly silent.

4.1.4 Speculative claims that seek protection well beyond the consideration given by the specification in its description of the invention are properly objected to for lack of fair basis. (The concept of "consideration given by the specification" is a concept relating to the contribution that a patent applicant gives to the public through the novel teachings in a patent application, in exchange for patent rights that the applicant receives from the public.) This inquiry is particularly relevant when a claim is broad, the ambit of the claim is indeterminate, and the field claimed is largely unexplored.

4.1.5 Claims that are open-ended and so broad as to cover processes or products unrelated to the process or product actually disclosed in the specification are objectionable for lack of fair basis.

4.1.6 If there is some feature in a claim to which no reference is made in the body of the specification, or if a claim is not limited by its terms to what the patentee has stated in the body of the specification to be the embodiment of the invention, then the claim is objectionable for lack of fair basis.

4.2. I was asked to review the Genentech application, the prosecution history, related documents published by Genentech' scientists and others, and the state of the common general knowledge at the time of filing, with the preceding guidelines in mind, and provide a scientific analysis relevant to the question of whether or not claims in the Genentech application are fairly based on the specification. My analysis above relating to insufficiency of the claims is relevant to this section, and is incorporated by reference. Additional particulars of my analysis follow.

B. **Analysis**

4.3. Upon careful consideration, I would conclude that at least claims 1-7, 9-15, and 28-38 (as well as claims which depend therefrom) of the Genentech application are not fairly based on the matter described in the specification to the extent that these claims: (a) can be interpreted to encompass an infinite number of deletional, insertional, or substitutional variants for which there is no description in the specification; or (b) can be interpreted to read on other growth factors bearing some relationship to VEGF (or polynucleotides encoding them) that exist in nature and were discovered by others and that are not identified in the specification and owe nothing to the teaching of the alleged invention; or (c) purport to define a polypeptide having a particular biological activity with respect to particular amino acid subsequences that have not been shown to confer the activity and do not confer the stated activity. It would appear that these claims represent an attempt to capture all possible solutions to a goal of providing a Flt4 ligand, even though the claims are supported by a much more limited teachings.

4.3.1 Claim 1 of the Genentech application recites, "Isolated biologically active human VEGF-related protein (VRP) containing at least 265 amino acids having the ability to bind and stimulate phosphorylation of a Flt4 receptor." Thus, claim 1 contains no limitation that is explicitly directed to a particular amino acid sequence, such as the VRP amino acid sequence taught in Figure 1 of the Genentech application. At least dependent claims 2-5, 9-15, and 23-28 contain no further limitation specifically directed to a particular sequence.

4.3.2 The Genentech application purports to include deletional, insertional, and substitutional variants within the definition of "human VRP." (See analysis in paragraph 2.2.1.1, repeated here by reference.) To the extent that Genentech asserts that variants not found in humans are within the definition of "human

VRP,"[4] the claim encompasses a potentially infinite number of deletional, insertional, or substitutional variants, none of which are described in the specification.

4.3.3 At least two naturally-occurring classes of proteins have been described in the literature which bring to light the discrepancy between the scope of what the Genentech application has claimed, and the scope of what the application actually discloses: non-human forms of VEGF-C, and human polypeptides encoded by genes other than the VRP gene.

4.3.3.1 For example, **Document D16**, International Patent Application No. PCT/US98/01973, filed on 2 February 1998 by Ludwig Institute for Cancer Research et al. (WO 98/33917), discloses sequences of murine and quail proteins (identified as "VEGF-C") that have significant sequence similarity to the VRP sequence in Figure 1 of the opposed patent. (**See Document D16** at Figures 5 & 10, for example.) At least the murine VEGF-C was shown to be a potent inducer of Flt4 (VEGFR-3) phosphorylation. (See **Document D16,** Example 26.) These proteins could be characterized as variants of the VRP sequence taught in Figure 1 of the Genentech patent application, in which a number of the VRP amino acids have been added, deleted, or replaced by other amino acids. However, these sequences owe nothing to the teachings of the

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[4] As set forth in paragraphs 5.4-5.4.3 relating to clarity, repeated here by reference, it is not clear whether the claims could be asserted to encompass non-human VRPs that were discovered by others and owe nothing to the specification of the Genentech application.

Genentech patent application. These sequences were discovered by other scientists working independently.[5]

4.3.3.2 Subsequent to the filing of the Genentech application, researchers who are not the inventors of the Genentech application have discovered at least one other human growth factor ("VEGF-D") that binds and stimulates phosphorylation of F1t4 receptor. (See discussion of VEGF-D at paragraphs 3.5.4-3.5.6, above, repeated here by reference.) VEGF-D has a different amino acid sequence from VRP and is encoded by a different human gene than the gene which encoded VRP taught in Figure 1 of the Genentech application. Although VEGF-D owes nothing to the specification of the Genentech application, Genentech might assert that the VEGF-D protein and cDNA satisfy claim 1 and dependent claims on the basis that VEGF-D matches the sequence of Figure 1 of the Genentech application, except for insertional, substitutional, and deletional variations, all of which are purportedly within the scope of the application's definition of "human VRP."

4.3.4 A third example is provided by the fact that the claims supposedly include VRP proteins (and polynucleotides) as large as 450 amino acids (codons) in length. As I explain in detail in paragraphs 3.2-3.2.2, repeated here by reference, the Genentech application teaches only a single VRP sequence that is only 419 amino acids in length. The idea of VRP as large as 450 amino acids is apparently nothing more than an unsolved goal.

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[5] The analysis in this paragraph is inapplicable if claim 1 is interpreted to cover only those polypeptides which are naturally expressed in human beings (due to the word "human" in claim 1).

4.3.5 The discrepancy between claim scope and supporting scientific disclosure is further exemplified by analysis of the biology behind Flt4 receptor binding and stimulation. Claims 6-7, 9-14, 19, and 23-28, at least, supposedly define a genus of biologically active VRP proteins (or polynucleotides encoding the biologically active VRP, vectors, or host cells) with reference to particular amino acid subsequences (*e.g.*, Figure 1, residues 1-29 or 1-137 or -20 to 29 or -20 to 137) that are insufficient to confer the specified biological activity of VRP (namely, the ability to bind and stimulate phosphorylation of a Flt4 receptor). I provided an annotated analysis of the residues required for Flt4 binding in paragraphs 3.6-3.6.5, above, which I repeat here by reference.

4.4 Another discrepancy between the scope of the claims and the teachings of the Genentech patent application is evident with respect to certain claims that pertain to receptor inhibition using biologically active VRP. In particular, claims 12 and 13 are directed to a method of using a biologically active VRP protein (as defined in earlier claims) to treat a dysfunctional state characterised by lack of inhibition of a VRP receptor. Treatment of a dysfunctional state characterised by lack of inhibition of a VRP receptor would require a therapeutic that inhibits the VRP receptor. However, the Genentech application provides no description of how to use biologically active VRP to inhibit VRP receptors. According to the application's stated definition for biological activity (page 5, last paragraph), VRP would be expected to aggravate a dysfunctional state characterized by lack of inhibition of a VRP receptor, because the VRP would further stimulate the receptor, rather than inhibit it.

4.5 A similar logic applies to claim 22, which is directed (in part) to a method of using a VRP antagonist to treat a dysfunctional state characterised by excessive inhibition of a receptor for VRP. The treatment of a dysfunctional state characterised by excessive inhibition of a VRP receptor would presumably require a therapeutic that activates the receptor, and it is unclear how a VRP antagonist would activate a VRP receptor and alleviate a dysfunctional state characterised by excessive inhibition of a VRP receptor. Since biologically active VRP stimulates VRP receptors (by definition), a VRP antagonist would prevent receptor activation, and thereby aggravate a

dysfunctional state characterized by excessive inhibition (i.e., insufficient activation) of the receptor.

4.6 Another discrepancy exists between the scope of claim 22 and its underlying support. Claim 22 is directed (in part) to a method of treating "Karposi's [sic] sarcoma." However, there is no scientific or medical reasoning or evidence provided in the Genentech application for believing that the alleged method of treatment would be beneficial for Kaposi's sarcoma.

4.7 Another discrepancy exists between the scope of "use" and "method" claims 12-13, 20, and 22, and the underlying support therefor. As explained in paragraphs 3.3-3.3.7.4, repeated here by reference, the Genentech application attempts to claim use of VRP or VRP inhibitors to treat a number of angiogenesis-related disorders, but teaches that VRP does not interact with known blood vessel receptors and instead interacts with the Flt4 receptor whose expression is taught to become restricted to lymphatic endothelia. There is a discrepancy between the biological activity taught for VRP and the dysfunctional states that the application indicates can be treated.

4.8 Another discrepancy between the scope of the claims and the teachings in the patent application is evident from Section 2 of this declaration, in which I describe why many claims are not novel over the prior art. An application that attempts to claim an invention that is not novel is attempting to claim more than the inventors truly provided to the public.

Lack of Clarity in the Claims

A. Introduction

5.1 I understand from my involvement in these proceedings that Australian patent law includes a "clarity" requirement. I understand that the claims of a patent are the portion that define the invention for which a patentee receives a monopoly, and the clarity requirement is a statutory obligation to state the invention clearly and distinctly in the claims. As part of my analysis of the Genentech application, I was asked to

evaluate whether the claims were clear to a skilled reader. I was told that certain guiding principles are relevant to any clarity analysis, including the following:

5.1.1 that any evaluation of clarity requires reading the claims in the context of the specification as a whole. For example, the specification may define claim terminology directly or aid in understanding claim terminology. My observations below were made while being mindful of the teachings and definitions provided in the specification of the Genentech application.

5.1.2 that another aspect of clarity focuses on internal consistency, *i.e.*, whether the invention defined in the claims is the same invention as that described in the specification. For example, features emphasized in the description, especially those described as critical or essential, should be included in each claim.

5.2 In my study of the Genentech application and its claims, I made several observations relevant to the issue of clarity, which I set forth below.

B. Analysis of the clarity of the claims of the Genentech application.

5.3 Claims 1-4, 9-17, 19-20, and 23-28, at least, lack clarity in that they recite a VEGF related protein (VRP) containing at least up to about 450 amino acids, but the application does not describe any VRP sequence longer than 419 amino acids.

5.3.1 I select this group of claims because dependent claims 2-4 explicitly recite VRP size ranges up to 450 amino acids. Independent claim 1 is apparently intended to be at least as broad as dependent claims 2-4, indicating that claim 1 also is supposed to encompass VRP of at least 450 amino acids. Claims 9-17, 19-20, and 23-28 depend from claims 1-4 without further restricting the length of VRP, indicating that they, too, are intended to encompass up to 450 amino acids..

5.3.2 The longest VRP sequences taught in the Genentech application are 419 amino acids (see, e.g., Figure 1). Thus, the structure of any VRP larger that 419 amino acids is unclear from the Genentech application.

5.4 Claims 1-28 lack clarity insofar as the metes and bounds of "human VEGF Related Protein" or "human VRP" are unclear.

5.4.1 The patent application purports to include deletional, insertional, and substitutional variants within the definition of "human VRP." (See Genentech application at page 5, lines 12-25.) It is unclear from the application whether the applicants intend the genus "human VRP" to encompass only the Figure 1 sequence and variants thereof that occur in human beings (i.e., allelic variants), or whether they intend the genus to cover the human sequence as shown in Figure 1 as well as any biologically active variant whatsoever (e.g., human allelic variants, non-human, naturally occurring VRP's, and synthetic molecules) whose sequence matches the Figure 1 imperfectly due to deletions, insertions, and/or substitutions.

5.4.2 To the extent that the patent applicant would assert that variants not found in humans are within the definition of "human VRP." the claim encompasses a potentially infinite number of deletional, insertional, or substitutional variants, none of which are described in the specification.

5.4.3 Even if the definition of "VRP" is restricted to human proteins, there are no apparent restrictions on the number of deletional, insertional, and substitutional variants within the definition of human VRP. Thus, it is unclear whether "VRP" is intended to read on completely different human proteins, such as VEGF-D, that bind and stimulate phosphorylation of Flt4 but are structurally distinct from the VRP disclosed in the patent application, e.g., in terms of length, amino acid sequence, and human gene of origin. (See my analysis at paragraphs 3.5.4-3.5.6, which I repeat here by reference.)

5.5 Claims 1-28 lack clarity insofar as the structure of a VRP cDNA and protein are unclear.

5.5.1 The claims pertain to VRP protein, polynucleotides, uses thereof, and the like. The chemical structure of the VRP protein and a cDNA (polynucleotide) encoding it are taught in Figure 1.

5.5.2 Figure 1 contains an ambiguity in that the codon "TAT" at codon position 94 of the cDNA encodes the amino acid tyrosine (Y). However, Figure 1 teaches that position 94 of the encoded VRP protein is a threonine (T). Thus, the chemical structure of the VRP cDNA, or VRP protein, or both, is unclear.

5.6 Claims 12-13, at least, lack clarity in that they seem to state that VRP has two diametrically opposed activities.

5.6.1 Claim 12 recites the use of a biologically active VRP protein according to Claims 1-8 for treating a dysfunctional state characterized by *either lack of activation or lack of inhibition* of a receptor for VRP.

5.6.2 It is unclear how biologically active VRP can be an effective medicament to treat both lack of activation and lack of inhibition of a VRP receptor, because activation and inhibition are opposite effects.

5.7 Claims 20 and 22 lack clarity in that they seem to state that VRP antibodies and VRP antagonists each have two, diametrically opposite therapeutic effects.

5.7.1 Claim 20 recites use of an antibody which binds biologically active VRP to treat a dysfunctional state characterized by *either excessive activation or inhibition* of a VRP receptor. Similarly, claim 22 recites a method for treating a dysfunctional state characterized by *either excessive activation or inhibition* of a VRP receptor with a VRP antagonist. (The application identifies VRP antibodies as VRP antagonists).

5.7.2 It is unclear how any VRP antagonist (or a VRP antibody in particular) can be an effective medicament to treat both excessive activation and excessive inhibition of a VRP receptor, because activation and inhibition are opposite effects.

5.8 Claims 1-28 lack clarity in that they purport to define an invention relating to human VRP but also appear to attempt to encompass an infinite set of variants, including VRP from non-human animals, that owe nothing to the teachings of the application.

5.8.1 Claim 1, the sole independent claim, recites "isolated biologically active human VEGF-related protein (VRP) containing at least 265 amino acids having the ability to bind and stimulate phosphorylation of a Flt4 receptor." All other claims depend from claim 1.

5.8.2 The specification teaches essentially one VRP protein and cDNA sequence of human origin (Figure 1).

5.8.3 However, the specification states that "human VRP" is defined as "a polypeptide sequence containing at least resides -20 to 399, inclusive, or residues +1 to 399, inclusive, of the amino acid sequence shown in Figure 1...as well as biologically active deletional, insertional, or substitutional variants of the above sequences having at least 265 amino acids . . . . (Specification at page 5, lines 12-25).

5.8.4 It is unclear from the specification whether the deletional, insertional, or substitutional variants must exist in nature in a living human in order for the variants to constitute "human VRP" as recited in the claims. If there is no such requirement, then it is unclear whether or not sequences which are derived from non-human animals and which contain some amino acids that are identical to Figure 1 and others that are deletional, insertional, or substitutional variation are considered "human VRP" (even though they are from non-humans). Likewise, it is unclear whether or not deletional, insertional, or

substitutional variations selected by scientists, which do not exist in any human or animal, are considered "human VRP" within the scope of the claim.

5.9 Claims 1-28 are unclear in their recitation of "biologically active" as a modifying term for VEGF-related protein.

5.9.1 The Genentech application states, "'Biologically active' for the purposes herein means having the ability to bind to, and stimulate the phosphorylation of, the Flt4 receptor." (See page 5, lines 26-27.) Even with this explicit definition, there is some ambiguity, because the next two sentences in the application seem to contemplate stimulation/activation or inhibition of the receptor and receptor-medicated activities. (See page 5, lines 27-30.) Activation and inhibition are generally considered to be opposites. It is unclear whether the applicants intended this continued discussion to be part of the definition of "biologically active."

5.9.2 Unlike other claims directed to "biologically active VEGF-related protein" (e.g., claims 7 and 8) claim 1 explicitly recites "biologically active **and** also recites "having the ability to bind and stimulate phosphorylation of a Flt4 receptor." It is unclear whether claim 1 is intentionally redundant in its recitations of "biologically active" and "ability to bind and stimulate phosphorylation of Flt4" or whether the applicants intend the term "biologically active" in claim 1 to have a different, non-redundant meaning.

5.9.3 Similarly, claim 16 is unclear in its recitation of "a biological activity of the protein [of any one of claims 1-8]." By virtue of the indefinite article "a," it is unclear if the applicant intends only the defined biological activity (Flt4 binding and phophorylation), or whether some other, undefined activity also would satisfy this limitation.

5.10 Claim 11 is unclear in its recitation of "a cell growth factor other than said protein." The metes and bounds of this term are unclear. The term is potentially broad enough to include oxygen, water, carbohydrates, salts, temperature, and other basic constituents of cell growth. Also, there exist factors that stimulate the growth of some cell types and inhibit the growth of other cell types, and it is unclear whether or not such factors would constitute "a cell growth factor other than said protein." If "cell growth factor other than said protein" is intended to refer to cell growth factors that are specific to cells that express VRP receptors, then it is unclear what, if any, growth

AUSTRALIA

Patents Act 1990

IN THE MATTER OF Australian Patent Application Serial No. 710696 by Genentech, Inc.

-and-

IN THE MATTER OF Opposition thereto by Ludwig Institute for Cancer Research

THIS IS Exhibit 1

referred to in the Statutory Declaration

of Peter Adrian Walton Rogers

made before me Elizabeth Jane Kennedy

DATED this 26th Day of October, 2000

Elizabeth Kennedy

Elizabeth Kennedy
B.A.LLB (Hons) LLM (Melb) SOLICITOR
Southern Health
246 Clayton Road Clayton
A natural person who is a current practitioner withir the meaning of the Legal Practice Act 1996

CURRICULUM VITAE

Peter Adrian Walton ROGERS

Department of Obstetrics & Gynaecology
Monash University
Monash Medical Centre
246 Clayton Road
Clayton Victoria 3168
Australia

PHONE:	+61-3-9594 5370
FAX:	+61-3-9594 5389
EMAIL:	PETER.ROGERS@med.monash.edu.au
HOME:	22 Lucan Street Caulfield North, Victoria 3161 Australia (Phone: +61-3-9527 7969)
DATE OF BIRTH:	1st September, 1955.
PLACE OF BIRTH:	London, England.
MARITAL STATUS:	Wife Cheryl and two children, Elizabeth 14 and Gillian 12
CITIZENSHIP:	Australian and British (Dual Nationality)
QUALIFICATIONS:	1977 BSc (Hons) 1983 PhD

1. EDUCATION

1966 - 1973

Abingdon School, Berkshire, UK

9 O-Levels, 3 A-levels.

September 1974 - June 1977

Liverpool University, U.K. B.Sc. Honours (IIA) in Marine Biology. Title of thesis: A Histological Study of Wound Healing in Plaice (Pleuronectes platessa).

2. POSTGRADUATE TRAINING

February 1980 - December 1982

Ph.D. studies, Flinders University, South Australia. Title of thesis: Rat Uterine Microvasculature During the Oestrous Cycle and Early Pregnancy.

March - June 1994

Mini sabbatical leave to work with Professor Steve Smith and Dr Stephen Charnock-Jones in the Department of Obstetrics and Gynaecology at Cambridge University. Studies included development of methods for non-isotopic techniques of in situ hybridisation and an investigation of VEGF expression in endometrium from women with progestin-induced breakthrough bleeding.

March-July 1988

Mini sabbatical leave to work with Prof. Gary Hodgen and Dr Ted Anderson at the Jones Institute Research Laboratories, Eastern Virginia Medical School, Norfolk, Virginia, USA. Studies included the development of a new technique for the isolation and long-term culture of human endometrial endothelial cells.

3. PREVIOUS RESEARCH POSITIONS

1993 -1995

NH&MRC Senior Research Fellow (levels 4-6), Dept. Obstetrics & Gynaecology, Monash University.

July 1986 - December 1992

Senior Research Fellow Grade 1. Dept. Obstetrics & Gynaecology, Monash University.

1985-1987

Worked on an intermittent basis as a scientific consultant for the company IVF Australia. Duties included advising on the establishment of IVF clinics in the United States, laboratory design and staff recruitment and training. During this period, numerous trips to the United States were made to provide training, technology transfer and assist in the process of opening new IVF clinics.

April 1985 - July 1987

Scientific Director of the Monash IVF Programme.

March 1985 - June 1986

Research Fellow Grade II, Dept. Obstetrics & Gynaecology, Monash University.

March 1983 - March 1985
Research Fellow Grade I, Department of Obstetrics & Gynaecology, Monash University.

December 1977 - December 1979
Research assistant to Dr. B.J. Gannon, Department of Human Morphology, School of Medicine, Flinders University, South Australia.

4. PRESENT APPOINTMENT

June 2000 to present: Director, Centre for Women's Health Research, Dept. Obstetrics & Gynaecology, Monash University
1998 to present: Associate Professor, Dept. Obstetrics & Gynaecology, Monash University
1996 to present: NH&MRC Principal Research Fellow, Dept. Obstetrics & Gynaecology, Monash University

5. COLLABORATIONS

As part of my work with the World Health Organisation Task Force on Long-Acting Systemic Agents for Fertility Regulation I am involved in several collaborative research projects with staff in the Human Reproduction Study Group at the University of Indonesia. The staff that I have the most involvement with are Dr Biran Affandi, Dr Sri Bekti Subakir, Dr Sugito Wonodirekso and Dr Julianto Witjaksono. This work investigates various aspects of endometrial breakthrough bleeding caused by long-term progestin contraception. This collaboration has been funded continuously by the World Health Organisation from 1990 with funds currently committed until the year 2000. I visit Jakarta 2-3 times per year where I am also involved in research training and technology transfer.

I collaborate with a number of people on different components of my research programme, including:
Dr Peter Dockery, University of Cork, Ireland; Morphometric studies on endometrial vasculature.
Dr Hillary Critchley, Edinburgh, UK. Menorrhagia studies.
Dr Chris Murphy, Dept. Anatomy & Histology, University of Sydney, Endometrial ultrastructure.
Dr Steve Stacker, Dr Marc Achen, Ludwig Institute, Melbourne. Various studies on VEGF
Dr Lois Salamonsen, Prince Henry's Institute, Melbourne. Norplant effects on the endometrium.
Prof. John Leeton, Monash IVF. Preparation of recipient endometrium for implantation
Dr Beatrice Susil. Anatomical Pathology, Monash Medical Centre. Endometrial and ovarian pathology.
Dr Euan Wallace. Dept. Obstetrics & Gynaecology, Monash University. Pre-eclampsia studies.
Dr Beverley Vollenhoven, Dept. Obstetrics & Gynaecology, Monash University. Fibroid studies.
Dr Paul Simmons and Dr Ivan Bertoncello, Stem Cell Laboratory, Peter MacCallum Cancer Institute.
Prof John Bertram, Dept of Anatomy, Monash University. Prof Bevyn Jarrot, Dept of Pharmacology, Monash University

"Exogenous hormones and dysfunctional bleeding." NIH, Bethesda, Maryland, USA. May 4-6th, 1992. Invited speaker.

VIIIth World Congress on Human Reproduction, Bali, Indonesia. April 4-9th. 1993. Basic studies on endometrial bleeding in norplant users.

14th Asian and Oceanic Congress of Obstetrics and Gynaecology, Manila, November 14-19th, 1993. Research on progestogen-induced vaginal bleeding: a collaboration between Indonesia and Australia.

31st May 1994; Department of Obstetrics and Gynaecology at Edinburgh University, "Vascular growth in normal and Norplant treated endometrium".

3rd June 1994; Department of Obstetrics and Gynaecology, Queens University of Belfast, "Angiogenesis in endometrial bleeding disorders".

First International Meeting of World Placenta Associations, October 24-28, 1994. Sydney. Invited plenary lecture: Current studies on human implantation.

Eighth Symposium of the Australian and New Zealand Microcirculation Society. Auckland, Feb. 3-5, 1995. Invited lecture: Reproductive angiogenesis.

Second International Symposium on IVF, Seoul, Korea, April 29-30, 1995. Invited lecture, "Maternal age effects on the endometrium."

World Health Organisation sponsored meeting in Bali, October 14-15th, 1995. "Current research on progestin-only contraceptives and endometrial bleeding".
International Ferring Symposium on Function and Dysfunction of the Non-Pregnant Uterus. A Satellite Symposium to the 1997 ESHRE Annual Meeting. Germany, June 19-21, 1997. Title: Endometrial microvascular growth in normal and dysfunctional states".

Group seminar at the Department of Surgery, Harvard University, Boston, USA. 14 August 1997. Title: "Angiogenesis in reproductive tissues".

WHO/NIH Symposium on Steroids and Endometrial Breakthrough Bleeding, May 4-5, 1999. Title:- Growth and regression of the endometrial vasculature.

Gordon Research Conference on Angiogenesis and Microcirculation, August 15-19, 1999. Rhode Island, USA. Chairman and Discussion Leader on Angiogenesis in Reproduction session.

Invitations To Speak In Australia And At National Meetings

Australian Society for Reproductive Biology. Embryo Transfer Satellite Symposium, Adelaide, 25th August 1985. Invited speaker.

Australian and New Zealand Microcirculation Society, Fifth Symposium, Canberra, 10-12th February, 1989. Invited Speaker.

The University of Melbourne, Department of Pharmacology, 26 April 1999. Title: "Angiogenesis in reproductive tissues".

Institute of Reproduction and Development Symposium, 7-8 May 1999. Title:-"Angiogenesis in ovarian cancer".

Monash University Department of Anatomy Seminar Series, August 4, 1999. Title:-Angiogenesis in reproductive tissues".

Awards

Australian Society for Fish Biology. Gilbert P. Whitley Memorial Award for best scientific presentation by a student. 1980 Annual Meeting.

Fertility Society of Australia, 5th Annual Scientific Meeting, Adelaide, December 1986. Serono-CSL award for best scientific presentation.

Fertility Society of Australia, 6th Annual Scientific Meeting, Sydney, November 1987. Merrell-Dow award for best poster presentation.

Australian and New Zealand Microcirculation Society. Best paper by a young scientist at 1989 meeting.

Awards Received By Group Members

Keren Abberton, PhD student. Australian and New Zealand Microcirculation Society. Best paper by a student at 1997 meeting

Maxine Orre, PhD student. Second Peter Mac Symposium. New Strategies for Cancer Detection and Therapy. Best poster award, 1997

Caroline Gargett, Postdoc. Tenth Australian and New Zealand Microcirculation Symposium. Best talk by a young scientist, 1999

Marina Zaitseva, Honours student. The Australian Society for Medical Research. Australian Vascular Biology Society. Young Investigator Award, 1999.

Caroline Gargett, Postdoc. Australian and New Zealand Microcirculation Society. The DG Garlic Award 1999.

Caroline Gargett, Postdoc. Australian Society for Reproductive Biology. Junior Scientist Award 2000.

7. POSTGRADUATE AND UNDERGRADUATE TEACHING

Completed Theses

PhD

1991-1994; Anne Macpherson. Title of Thesis: Endometrial angiogenesis

Regulation of VEGF receptors in human endothelial cells.
Sophie Gohl; Topic of Thesis: Investigation of fibroid and myometrial smooth muscle cell physiology using the cytocensor.
Lara Gambino; Topic of Thesis: Mechanisms of angiogenesis in human endometrium.

Undergraduate Teaching Experience

At Monash University I give a limited number of lectures to students in the Diploma and Masters of Reproductive Science courses, as well as providing supervision for various assignments and a practical class on immunohistochemistry. In the past I have given occasional lectures to the 5th year medical students, as well as to physiology, anatomy and veterinary students. At Flinders University from 1978-1982 I was heavily involved in running first year biology practical classes, as well as demonstrating anatomy and histology to medical students.

8. ADMINISTRATIVE RESPONSIBILITIES

Community Service: Trustee for the Jean Hailes Menopause Foundation (1988 to present)
In 1988 I became involved with 5 other people in establishing the Jean Hailes Foundation in honour of the life work of Dr Jean Hailes who died in November of that year. The Jean Hailes Foundation is a non-profit organisation specialising in the management of women's health. The Trust under which the Foundation operates, specifies 3 major activities:- clinical services, research, and education, with the latter having a strong focus on health promotion and illness prevention. Since the opening of the Clinic in 1992, the Foundation and its activities have grown at a dramatic rate. In the financial year 1997-1998, the Foundation had a turnover in excess of $1.7million. As one of five Trustees, I take responsibility for a range of policy and financial issues within the organisation. I have represented the Jean Hailes Foundation in discussions with both State and Federal Health Ministers and the work of the Foundation enjoys strong recognition from both these levels of government. Among the many activities currently on the agenda at the Foundation is the establishment of the Jean Hailes Chair in Women's Health to be established in the Monash University Department of Obstetrics and Gynaecology with funds raised by the Jean Hailes Foundation.

Committee Memberships And Management Contributions

1999 to present	Faculty of Medicine Research Strategic Planning Committee (Sub-committee of the Faculty of Medicine Research Committee)
1996 to present	Chairman, Department of Obstetrics and Gynaecology postgraduate students committee
1995 to present	Department of Obstetrics and Gynaecology Executive and Finance Committee
1992 to present	Company Director for Menoserve Pty Ltd, trading entity for the Jean Hailes Menopause Foundation.
1989 to present	Trustee and Foundation Board member of The Jean Hailes Menopause Foundation Trust.

1988 to present	Scientific Director, Monash IVF Donor oocyte program.
1988 to present	Department of Obstetrics and Gynaecology monthly Academics meetings.
1996 - 1998	Chairman. Monash Medical Centre Animal Experimentation Ethics Committee
1987 - 1998	Member, Monash Medical Centre Animal Ethics Committee
1997	Member, Monash University Animal Welfare Committee
1995 - 1997	Member, Faculty of Medicine B. Med. Sci. Committee
1993 - 1997	Member, Institute of Reproduction and Development Executive.
1993 - 1997	Department of Obstetrics and Gynaecology representative on Monash University Faculty of Medicine Board.
1989 - 1997	Board Member, Monash University Centre for Reproductive Biology
1986 - 1988	Member, Queen Victoria and Monash Medical Centre Animal House Co-ordinating Committee
1987 - 1988	Member, Monash Medical Centre IVF Unit Executive
1985 - 1987	Monash University-IVFA Operations Committee
1984 - 1987	Member of Monash IVF Executive
1984 - 1987	Member of Monash IVF Finance Committee
1985 - 1986	Chairman, Obstetrics & Gynaecology Animal Ethics Committee
1984 - 1985	Obstetrics & Gynaecology Representative on University Biomedical Library Committee
1981 - 1982	Postgraduate Representative on Flinders Medical Centre School Board
1981 - 1982	Member. Flinders Medical Centre Audio Visual Advisory Committee
1982	President, Flinders University Sports Association
1980 - 1982	President, Flinders University Underwater Club
1983 - 1986	National Testing Officer, Cave Diving Association of Australia

9. PEER REVIEW AND SCIENTIFIC DISCIPLINE INVOLVEMENT

Refereeing For International Journals And Granting Bodies

I am on the editorial board of the new international journal, Angiogenesis, and have served on the Editorial Board for the Chinese Journal of Physiology. I have acted as an ad hoc referee for a number of scientific journals, including: Journal of Reproduction and Fertility, Biology of Reproduction, Fertility and Sterility, Human Reproduction, Human Reproduction Update, Molecular Human Reproduction, Reproduction Fertility and Development, Journal of Endocrinology and International Journal of Cancer.

I referee grant applications for numerous agencies including National Health and Medical Research Council, Australian Research Council, various Australian Anti Cancer agencies, the Wellcome Foundation, the Health Research Council of New Zealand and the Biotechnology and Biological Sciences Research Council. In February 1999 I was a scientific grant referee for Indonesian Ministry of Education and Culture, Directorate General of Higher Education

Society Memberships

Australian Society for Reproductive Biology
Australian Society for Medical Research
Australian Fertility Society (Foundation member)
Australian & New Zealand Microcirculation Society (Foundation member and President 1997-1998)
American Society for Reproductive Medicine (Formerly The American Fertility Society)
Society for the Study of Reproduction (USA)

Scientific Committee Memberships And Society Offices Held

1998 - 1999	Chairman, Organising committee for WHO/NIH symposium on contraceptives and endometrial bleeding to be held at Monash Medical Centre May 4-5, 1999
1998 - 1999	Chairman, Organising Committee for Institute of Reproduction and Development annual symposium. "Angiogenesis in Reproductive Tissues" to be held at Monash Medical Centre May 7-8, 1999.
1997 – 1998	President, Australia and New Zealand Microcirculation Society
1996 - 1997	Chairman of organising committee for 1997 Australian and New Zealand Microcirculation Society Conference in Melbourne, January 30 - February 1, 1997.
1994	Member of organising committee, Carl Wood Festschrift, "Reproductive medicine beyond 2000".
1994	Convenor, Scientific Program Organising Committee, Australian Society for Medical Research 33rd National Scientific Conference, Melbourne, 27-30 November 1994

1992	Convenor, Victorian ASMR Medical Research Week.
1991	Lecture program organiser, Victorian ASMR Medical Research Week.
1990-1991	Organising committee and session chairman, Australian and New Zealand Microcirculation Society 1991 Scientific Meeting.
1989	Organiser and Chairman, Fertility Society of Australia Embryology Symposium
1985	Organizing Committee, 4th World Congress on IVF, Melbourne, Australia

10. RESEARCH GRANT SUPPORT

I continue to run a group of between 10 and 15 staff and students with 80% of funding being obtained from peer review national and international sources. Over the 5 years, 1994-1998 I attracted approximately $1.6 million in outside research funds, and my research group published 46 peer review publications, 14 chapters or invited reviews, and 53 conference abstracts.

Research Grants And Funding To Dr. P.A.W. Rogers

1985	Special research grant, Monash University. The role of the uterine microvasculature in early implantation	$7,500
1985	Special grant from Serono and Commonwealth Serum Laboratories towards the establishment of a departmental histology laboratory	$28,000
1985	Special grant of equipment towards the development of a high purity water system for IVF application from Millipore Australia	$20,000
1985	Special grant from Organon towards a technical assistant's salary	$10,000
1985	Donation from IVF patient towards microscope equipment for histology laboratory	$6,000
1986-1988	NH&MRC. In vivo and ultrastructural studies on implantation and uterine receptivity	$116,285
1986	William Buckland Foundation. Histological investigation of the anterior eye chamber embryo implantation model	$3,060
1986	Special Research Grant, Monash University. Ultrastructural studies of human endometrium relating to uterine receptivity for implantation	$5,000
1987	NH&MRC. Application for an electron microscope for studies in reproduction. Chief Investigator: Dr. A. Trounson, Senior Investigators: Drs. P. Rogers, A. Walker, H. Sathananthan	$87,000

1987	Clive and Vera Ramaciotti Foundation. Shared equipment for measuring red blood cell velocity from videotape records of intravital blood flow in the micro-circulation. (Other Chief Investigators: Prof. B. Gannon, Prof. P. O'Brien)	$10,000
1987	William Cook Australia Pty. Ltd. Technical salary support	$5,000
1987	R.A. Hallenstein Charitable Trust. The role of uterine factors in human infertility	$1,000
1988	Brockhoff Foundation. Ultrastructural studies on human post-menopausal endometrium following steroid replacement therapy	$26,144
1988	R.A. Hallenstein Charitable Trust	$3,000
1989-1991	NH&MRC. Molecular changes in the plasma membrane of human uterine epithelial cells	$90,150
1989	CONRAD. Isolation and culture of human endometrial endothelial cells	$18,797
1989	R. A. Hallenstein Charitable Trust	$3,000
1989	Monash Research Fund. Endometrial response to different postmenopausal hormone replacement therapies	$2,550
1990	Monash Medical Centre. Endometrial microvascular response to oestrogen	$3,000
1990	Sunshine Foundation. Endometrial microvascular response to oestrogen	$5,000
1990	Perpetual Executors and Trustees. Endometrial microvascular response to oestrogen	$5,000
1990	Helen Schutt Foundation. Endometrial vascular response to oestrogen	$5,000
1990	Infertility Medical Centre. Correlation of endometrial histology, morphometry and ultrasound appearance with superovulation protocol for IVF	$12,000
1990-1993	World Health Organisation. The aetiology of increased endometrial bleeding in Norplant users; the role of local factors	$300,000
1990	Buckland Foundation. Endometrial vascular response to oestrogen	$5,000

1990	R. A. Hallenstein Charitable Trust. Endometrial vascular response to oestrogen	$3,000
1990	Collier Charitable Fund. Equipment grant to purchase a microhysteroscope for O&G Dept	$2,500
1991-1993	NH&MRC. A study of endometrial microvascular function during embryo implantation	$219,663
1991-1993	NH&MRC. The role of local endometrial factors in perimenopausal uterine bleeding	$190,937
1991	Helen M. Schutt Trust. Equipment grant to purchase a microhysteroscope for O&G Dept	$3,000
1991	William Angliss Charitable Fund. Equipment grant to purchase a microhysteroscope for O&G Dept	$2,000
1992	Collier Charitable Fund. Purchase of 2 chemotaxis chambers	$2,250
1992	Sunshine Foundation, Equipment grant to purchase a set of objective lenses for a new microscope	$4,828
1993-1997	NH&MRC. Local regulation of endometrial angiogenesis (Senior Research Fellowship)	$211,745
1993-1995	NH&MRC. Local mechanisms influencing endometrial function in menorrhagia	$189,753
1993	Collier Charitable Trust. Purchase of image scanner	$2,750
1993	ANZ Trustees. Purchase of Zeiss microscope	$10,000
1993	ANZ Trustees. Menstrual disorders, Impact on womens health	$10,000
1994-1996	World Health Organisation. Local control of the endometrial vasculature in women receiving long-term progestogen contraception	$254,000
1994-1995	Anti-Cancer Council of Victoria. Role of vascular endothelial growthfactor in ovarian tumour angiogenesis	$64,000
1994-1995	Slezak Trust (Through The Jean Hailes Menopause Foundation). Control of vascular growth in ovarian cancer	$102,000
1994	The Arthur Wilson Memorial Scholarship in Obstetrics & Gynaecology. Spiral arteriole development in menorrhagia (Awarded to Dr Jacoba Kooy, postdoc in group)	$20,000

1994	British Council Travel Grant. Travel funds for UK sabbatical	$2,299
1994	Wellcome-Ramaciotti Research Travel Grant.	$1,500
1994	William Buckland. The mechanism of action of Danazol in the regression of human endometrium and microvascular density. (Awarded to Dr. Tseng Lau, postdoc in group).	$12,750
1995-1997	NH&MRC. Uterine microvascular-embryo interactions during implantation in the rat	$163,818
1996-1998	The Jean Hailes Menopause Foundation. Research support grant.	$15,000
1997	The Royal Australian College of Obstetrics & Gynaecologists. Arthur Wilson Memorial Scholarship in Obstetrics & Gynaecology.	$20,000
1996-2000	NH&MRC. Endometrial angiogenesis (Principal Research Fellowship Grant)	$958,883
1998-2000	World Health Organisation. Investigation of local mechanisms associated with progestin induced endometrial bleeding	$252,392
1998	Appel Family Bequest. Factors influencing fibroid growth and Development.	$12,500
1998	Contract Research with Kryocor Pty Ltd. Funds to establish endothelial Cell laboratory	$42,000
2000-2004	NH&MRC. Endometrial angiogenesis. Principal Research Fellowship grant.	$1,175,000

11. BRIEF OUTLINE OF PREVIOUS, CURRENT AND PROPOSED RESEARCH EXPERIENCE

1977-1979

Work as Research Assistant in laboratory of Dr B Gannon, Dept. Human Morphology, Flinders University. Projects included histology, ultrastructure, morphometry and vascular corrosion casting studies on the microvasculature of the mammalian small intestine, lungfish gills and tuna gills.

1980-1983

PhD studies on rat uterine microvascular structure and function. Techniques included ultrastructure, vascular corrosion casting, morphometry and in vivo microscopy.

1983-1985

Postdoctoral appointment with Monash IVF. During this period I gained expertise in all aspects of human IVF, including embryology, andrology, endocrinology, ovulation induction and cryopreservation. In addition, I obtained independent research funding for staff and equipment to establish my own basic endometrial/implantation research group.

1985-1987
Scientific Director, Monash IVF. Duties included overseeing and co-ordinating the scientific research projects associated with the Monash IVF programme, running the embryology laboratory, maintaining quality control and ensuring an adequate pregnancy rate, recruiting, training and supervising embryology staff (the IVF programme employed 6 embryologists at this time), preparing and participating in public information seminars and debates, and preparing submissions for government committees reviewing the legislation controlling and the funding for IVF in Australia. During this period I also ran my own basic research group studying endometrial function and implantation, and in 1986 obtained project funding from NH&MRC for studies on embryo implantation.

1988-1992
My primary activities during this period were obtaining funding for, and running, a number of basic research projects relating to menstruation, the pathology of abnormal uterine bleeding, embryo implantation, endometrial structure and function and the endometrial microvasculature. Specific research projects included; work on endometrial microvascular function in women using long-term progestin contraceptive implants, factors that cause increased endometrial bleeding in peri-menopausal women, and the response of the rodent endometrial microvasculature to the implanting embryo.

1993-1996
Major research interests included endometrial physiology, microvascular function, angiogenesis, and embryo implantation as well as a number of relevant gynaecological disorders including menorrhagia, endometriosis, peri-menopausal problems and contraceptive induced break-through bleeding. Developed considerable expertise in immunohistochemistry methodology.

1997- to present
My research interests continued to develop within the broad field of reproductive biology and angiogenesis. Specific interests include understanding of the mechanisms and regulation of physiological angiogenesis in reproductive tissues during the menstrual cycle, and alterations in the angiogenic process that occur in tumour tissues. A number of collaborations with clinical investigators within and associated with the Department of Obstetrics and Gynaecology include work on topics such as leiomyoma, interstitial cystitis, endometriosis, menorrhagia, and pre-eclampsia. More recently I have established an endothelial cell laboratory in conjunction with an industry partner with various projects investigating macro and micro vascular endothelial cell biology.

The Future
I will continue to develop the expertise within my group and the Obstetrics & Gynaecology Department to pursue basic studies in areas such as angiogenesis, endothelial cell biology, and microvascular function. More clinically oriented studies will continue into diseases such as

reproductive cancers, menorrhagia, endometriosis, leiomyoma, interstitial cystitis, and pre-eclampsia. We have developed significant expertise in techniques such as immunohistochemistry, image analysis and tissue culture (including isolation and culture of microvascular endothelial cells, and a range of primary cell separation and culture techniques). Another major strength is our ability to liaise with a large number of clinical staff both in Melbourne and overseas. This gives us rapid access to large collections of well characterised clinical material for our research studies. We also have capabilities in a range of other methodologies, including in situ hybridisation, PCR, Northerns, RPA and various biochemical techniques. The development and increasing contribution of Dr Caroline Gargett as a postdoc within the group is seen as a significant plus for the future. Similarly, the recent addition of Dr Euan Wallace as a specialist obstetrician and researcher to the Department has opened up major new opportunities for collaboration. At the present time these are being pursued in the form of a major research proposal on pre-eclampsia.

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COMMONWEALTH OF AUSTRALIA

IN THE MATTER OF : Australian Patent Application 696764 (73941/94). In the name of: Human Genome Sciences Inc.

-and-

IN THE MATTER OF: Opposition thereto by Ludwig Institute for Cancer Research, under Section 59 of the Patents Act.

STATUTORY DECLARATION

I, Stuart A. Aaronson of Mount Sinai Medical Center, New York, New York, United States of America, declare as follows:

1. I have been asked by the Patent Attorneys representing Human Genome Sciences ("HGS") to serve as a scientific consultant in connection with the Ludwig Institute for Cancer Research Opposition to the issuance of HGS Australian Patent Application 696764, in the name of HGS, entitled: "Vascular Endothelial Growth Factor-2" ("the HGS patent specification").

2. In acting as a scientific consultant for HGS, I provided a Statutory Declaration executed December 14, 2000 ("Aaronson Declaration I") in connection with the Opposition of the HGS patent specification, in which I provided my comments and opinions on what the HGS patent specification would provide to one skilled in the field of molecular biology of growth factors, *e.g.*, a post doctorate or Ph.D. candidate in a research laboratory, and to provide my comments and opinions on the experimental evidence provided in Dr. Alitalo's Statutory Declaration executed on February 15, 2000 ("Alitalo Declaration I"). I have now been asked by the Patent Attorneys representing HGS to review and provide comments on the Statutory Declaration executed by Dr. Alitalo on September 14, 2001 ("Alitalo Declaration II").

3. The HGS patent specification relates to the identification and characterization of a new member of the PDGF/VEGF family of growth factors, VEGF-2, which is also known as VEGF-C. VEGF-2 and VEGF-C are recognized to be identical proteins by those working in the field, as they have nearly identical sequences as demonstrated by the sequence alignment, appendixed hereto as Appendix I.

4. In providing my comments and opinions, I have been asked to keep in mind what the HGS patent specification would provide to one familiar with the molecular biology of growth factors as of the earliest filing date of the HGS patent specification, which I have been told is March 1994. For purposes of this analysis, I considered and give an opinion on not only what I knew and appreciated at the relevant time, but also what was expected to be known by one skilled in the field of the molecular biology of growth factors, such as graduate students and postdoctoral fellows who were in my laboratory at the relevant time. The opinions I express are, unless I state to the contrary, opinions based upon these considerations and they would have been applicable as of March 1994, the filing date of the HGS patent specification, as of September 1995, the publication date of the HGS patent specification and are also applicable now. Further, despite the fact that many of my opinions have been presented in the present tense for the ease of expression, I would have held those opinions in March 1994.

5. Dr. Alitalo attempts to provide new experimental data that allegedly addresses the criticisms raised by the HGS scientific consultants of the experimental evidence provided in Alitalo Declaration I. Dr. Alitalo further purports to analyze the expression, proteolytic processing, and secretion profiles of VEGF-2 as taught in the HGS patent specification. However, due to numerous defects in the design, performance, and analysis of these new experiments, the results presented in Alitalo Declaration II fail to provide any

meaningful information regarding the expression, processing and secretion of VEGF-2 as taught in the HGS patent specification. For example, I have identified the following deficiencies in Alitalo Declaration II:

- The failure to follow the teachings of the HGS patent specification as a whole when designing the new experiments;
- The inability to refute that, by following the teachings of the HGS patent specification, the 350 amino acid VEGF-2 protein results in the correct expression, secretion, and processing of the mature form of VEGF-2;
- The failure to design experiments to result in meaningful conclusions with respect to the teachings of the HGS patent specification; and
- The failure to draw credible or consistent conclusions based on the new experiments regarding the expression, processing and secretion of VEGF-2 as taught in the HGS patent specification.

The following paragraphs detail these deficiencies identified in the Alitalo Declaration II.

The Alitalo Declaration II Fails to Follow the Teachings of the HGS Patent Specification as a Whole

6. Dr. Alitalo purports that his new experiments were designed to determine whether utilizing the teachings provided in the HGS patent specification, the 350 amino acid form of VEGF-2 is expressed, processed and secreted. However, the experimental procedures set out in Alitalo Declaration II fail to correct one of the critical flaws of Alitalo Declaration I, *i.e.*, it fails to follow the teachings of the HGS patent specification. In particular, Dr. Alitalo's new experimental design is flawed because he fails to recognize that the HGS patent specification specifically provides that the 350 amino acid sequence may be expressed with a heterologous signal sequence.

7. Likewise, Dr. Alitalo fails to recognize that the experiments described in the Statutory Declaration executed by Susan Powers on December 20, 2000 ("Power Declaration I") demonstrated that VEGF-2 could be expressed, processed and secreted. In particular, Dr. Power's experiments demonstrated that the 350 amino acid form of VEGF-2 can be expressed, processed and secreted from cells when attached to a heterologous signal sequence as specifically taught by the HGS patent specification. (*see* HGS patent specification at page 14, lines 6 to 19).

8. In particular, Dr. Alitalo fails to acknowledge that the HGS patent specification specifically teaches the construction of expression vectors which comprise the 350 amino acid sequence of VEGF-2 fused in frame with a signal sequence. The HGS patent specification provides:

> Generally, recombinant expression vectors will include . . . . [t]he heterologous structural sequence [is] assembled in appropriate phase with translation initiation and termination sequences, and preferably, *a leader sequence* capable of directing secretion of translated protein into the periplasmic space or extracellular medium. (*see* the HGS patent specification at page 14, lines 6 to 19, emphasis added).

9. Dr. Alitalo has ignored the teaching of the HGS patent specification and has taken the position that no one familiar with the molecular biology of growth factors would utilize a heterologous signal sequence to achieve secretion of a secretory protein which has been identified to have a putative signal sequence. By following the teachings of the HGS patent specification, I believe I or a skilled molecular biologist could utilize a heterologous signal sequence in order to express, process and secrete the 350 amino acid form of VEGF-2.

10. Indeed, contrary to Dr. Alitalo's statements in Alitalo Declaration II, utilizing a heterologous signal sequence is clearly the approach that would be taken by

one familiar with the molecular biology of growth factors. One familiar with the molecular biology of growth factors equipped with the HGS patent specification would recognize that the 350 amino acid polypeptide is a secreted growth factor, and that if the 350 amino acid sequence did indeed contain a signal sequence such a sequence does not have the typical conserved motif of a signal sequence. Thus, if upon expression of the 350 amino acid form of VEGF-2, secretion of the protein did not occur, a skilled molecular biologist would utilize a strong signal sequence to ensure expression and secretion of the protein. Thus, Dr. Alitalo has taken a position which not only is clearly inconsistent with the teachings of the HGS patent specification, but is also contrary to the approach that the skilled molecular biologist would utilize.

11. Dr. Alitalo not only clearly ignores the literal teaching of the HGS patent specification which describes VEGF-2 as a secreted growth factor (*see, e.g.* HGS patent specification at page 5, lines 25 to 33), but incorrectly attributes this recognition to his own research conducted two years subsequent to the filing date of the HGS patent specification (*see* Alitalo Declaration II ¶ 2.2). Contrary to Dr. Alitalo's statements in Alitalo Declaration II, the HGS patent specification filed March 1994 accurately characterizes VEGF-2 as another member of the PDGF/VEGF family of secreted growth factors.

12. In summary, Dr. Alitalo's failure to follow the teachings of the HGS patent specification in designing the experiments provided in Alitalo Declaration II prevents any meaningful conclusions from being drawn about the expression, proteolytic processing and secretion of VEGF-2 as taught in the HGS patent specification.

The Alitalo Declaration II Fails to Refute that by Following the Teachings of the HGS Patent Specification the 350 Amino Acid VEGF-2 Protein Results in the Correct Expression, Secretion, and Processing of the Mature Form of VEGF-2.

13. In my opinion, Dr. Alitalo fails to provide experimental evidence to contradict the fact that the 350 amino acid VEGF-2 fused in frame with a heterologous signal sequence results in the expression, secretion and proteolytic processing of a mature form of VEGF-2.

14. In Alitalo Declaration II, Dr. Alitalo *newly* raises the issue that the HGS patent specification does not provide a description of the molecular weight of the approximately 30 kDa doublet. (*see* Alitalo Declaration II, ¶5.6).

15. One knowledgeable in the field of molecular biology would not require that the HGS patent specification provide the molecular weight of the secreted form of VEGF-2. Clearly, in following the teachings of the HGS patent specification, as demonstrated by Power Declaration I and Susan Power's Second Declaration ("Power Declaration II"), I or a molecular biologist would recognize that the 350 amino acid sequence of VEGF-2 can be processed to a mature form of VEGF-2 by the cell. Therefore, a molecular biologist provided with the teaching of the HGS patent specification would be able to express VEGF-2 as its naturally processed mature form. Further, a molecular biologist provided with the teaching of the HGS patent specification would recognize that the molecular weight of the resulting processed mature form of VEGF-2 is an intrinsic and natural property of that molecule.

16. Besides molecular weight, the amino acid sequence of a particular protein is also an inherent property of that protein. Statements that Dr Heldin, an apparent colleague of Dr. Alitalo, has made in support of the prosecution of Dr. Alitalo's U.S. Patent No. 6,221,839 are in agreement with this conclusion.

In particular, Dr. Heldin has stated: "It is fundamental biochemistry that polypeptides are organic chemical compounds, albeit sometimes large and complex ones. Like all organic chemical compounds, polypeptides may be characterized by any of *several inherent physical properties, such as molecular formula and molecular weight*. Such physical properties are inherent characteristics of organic molecules in that they are intrinsic properties of the molecules. Because polypeptides are themselves composed of covalently-bonded chains of smaller organic moieties called amino acids (of which there are about 20 naturally occurring), it is conventional to express the molecular formula of polypeptides as an amino acid sequence. *The amino acid sequence of any polypeptide is an inherent property of that polypeptide*." (*see*, the Declaration by Dr. Carl-Henrik Heldin, executed June 4, 1997, provided to the U.S. Patent & Trademark Office during prosecution of U.S. Patent No. 6,221,839, the "Heldin Declaration", at page 6, emphasis added).

17. Thus, I or a molecular biologist following the teachings of the HGS patent specification to express the 350 amino acid VEGF-2 polypeptide would recognize that the molecular weight and the amino acid sequence of the naturally processed and secreted form of VEGF-2 is an inherent feature of that polypeptide. Hence, it would be unnecessary for the HGS patent specification to have reported the molecular weight of the 30kDa doublet and 23kDa secreted forms of VEGF-2, because I or a molecular biologist, just like Dr. Heldin, would recognize that the molecular weight and the amino acid sequence is an inherent property of the 350 amino acid form of VEGF-2.

18. Additionally, the Alitalo Declaration II *newly* raises the issue that the processing of the 350 amino acid protein as taught by the HGS patent specification would be incorrect. (*see e.g.,* Alitalo Declaration II ¶ 3.7 or ¶ 5.5).

19. The only information and signals required by a host cell to express and process VEGF-2 to its mature form is contained in the amino acid sequence of VEGF-2. Any given host cell, *i.e.*, a mammalian host cell, will have the proteolytic enzymes and cellular machinery to naturally process VEGF-2 to its mature form. Thus, following the teachings of the HGS specification, the 350 amino acid VEGF-2 polypeptide is naturally and intrinsically processed to its mature form, as demonstrated by the results presented in Power Declaration I and II.

20. I have reviewed and agree with the characterization of the inherent features of the processing of a biologically active mature form of VEGF-2 as provided by Dr. Alitalo himself in portions of the file histories of U.S. Patent Nos. 6,221,839 and 6,245,530.

21. Accordingly, Dr. Alitalo has characterized the processing of VEGF-2 from various cell types, including both mammalian and insect expression systems and has observed that VEGF-2 is intrinsically and naturally processed to its mature form in a wide variety of cell types. (*See,* Declaration by Dr. Kari Alitalo, provided to the US. Patent & Trademark Office on June 10, 2000, in connection with prosecution of U.S. Patent No. 6,245,530, issued June 12, 2001). Evidence of the intrinsic and natural processing of the polypeptide is further confirmed by the observations that the expression of the full length and portions of VEGF-2 in various cell types results in the processing and secretion of a biologically active mature form of VEGF-2. Indeed, Dr. Alitalo has observed that the expression of polypeptides corresponding to residues 104 to 213 and 112 to 419 of the full length VEGF-2 polypeptide are correctly processed to mature forms of VEGF-2 that retain VEGF-2 biological activity. (*See*, Declaration by Dr. Kari Alitalo, provided to the U.S. Patent & Trademark Office on December 1, 1997, in connection with the prosecution of U.S. Patent No. 6,245,530; *see also*, Declaration by Dr. Kari Alitalo, provided to the U.S. Patent & Trademark Office on July 24, 2000, in connection with

the prosecution of U.S. Patent No. 6,221,839; the file histories of both U.S. Patents are annexed hereto as Appendices II and III, respectively).

22. Thus, as Dr. Alitalo has concluded, I or a molecular biologist would also conclude that the full length and portions of the VEGF-2 polypeptide are intrinsically and naturally processed to a biologically active mature form. Likewise, when appropriately expressed as taught by the HGS patent specification, the 350 amino acid form of VEGF-2 contains all of the signals required for the processing of the protein to its biologically active mature form.

The Alitalo Declaration II Fails to Design Experiments that Allows for Meaningful Conclusions with Respect to the Analysis of VEGF-2 as Taught in the HGS Patent Specification.

23. Dr. Alitalo indicates that the experiments reported in Alitalo Declaration II confirm the results of the experiments in Alitalo Declaration I and eliminate any criticisms of the experimental design described in Alitalo Declaration I. However, the criticisms of the experimental design described in Alitalo Declaration II have not been addressed because the experimental design reported in Alitalo Declaration II is also flawed and cannot support any conclusions made with respect to the expression, secretion and processing of VEGF-2 as taught in the HGS patent specification. In particular, the experiments reported in Alitalo Declaration II fail to include experimental controls to address any potential problems with expression vectors, cells, transfection, and conditions and parameters which might affect the comparative analysis of the 350 amino acid VEGF-2 and the 419 amino acid VEGF-2. I discuss these faulty experiments below.

24. Dr. Altilo's conclusions regarding the level of expression of 350 amino acid form of VEGF-2 as compared to the expression of 419 amino acid form of VEGF-2 are meaningless because no experiments were conducted to

determine the transfection efficiency of the plasmids used -- thus preventing the drawing of any valid quantitative comparisons regarding expression efficiencies from the data obtained. Disparate parameters such as cell densities or growth conditions can affect the transfection efficiency of expression constructs into cells. The transfection efficiency will directly correlate with the level of protein expression detected. Clearly if fewer cells contain the construct, fewer cells will express the protein encoded by the construct. Accordingly, any differences in the relative transfection efficiency of the VEGF-2 plasmids utilized in Dr. Alitalo's experiments would affect the comparative detection of levels of VEGF-2 protein. Dr. Alitalo does not provide experiments to demonstrate that following transfection, the same percentage of cells contained each expression construct. In fact, if the transfection efficiency of the 350 amino acid form of VEGF-2 were very low, very few cells would produce protein expressed from the construct and expression and secretion of VEGF-2 protein would be difficult to detect. Without determining transfection efficiency, any conclusion about levels of protein expressed and detected is meaningless.

25. Dr. Alitalo also speculates that the VEGF-2 as taught in the HGS patent specification is not secreted, but rather is rapidly degraded in cells. (*see* Alitalo Declaration II ¶ 3.9). This speculation has not been affirmatively confirmed by any of the experimental results described in Alitalo Declaration II. Assuming *arguendo* that normally secreted VEGF-2 is rapidly degraded in the cell, then any additional time period that passes before cells are assayed for the presence of VEGF-2 protein would result in the inability to detect the presence of VEGF-2 protein. Furthermore, the experimental protocol described in Alitalo Declaration II does not allow for detection of VEGF-2 protein expression over various time points. Rather, protein levels are assessed fifty hours post-transfection (forty-eight hours and overnight metabolic labeling). Without allowing for the detection of VEGF-2 protein that is purportedly expressed yet degraded with the passage of time over

various periods of time, the conclusions of Dr. Alitalo regarding expression and degradation are merely speculative.

The Alitalo Declaration II Fails to Draw Credible Conclusions with Respect to the Expression, Secretion and Processing of VEGF-2 as Taught in the HGS Patent Specification.

26. In summary, the flaws introduced into the experimental design and protocols of Dr. Alitalo render the experimental results inconclusive. As discussed above, in the absence of appropriate controls, comparative analysis is meaningless because disparate conditions and parameters will affect the expression, secretion and processing profiles of 350 amino acid VEGF-2 and 419 amino acid VEGF-2. In any comparative analysis, results are meaningless without the assurance that unnecessary variables are eliminated. The failure to include basic experimental controls to ascertain that there would be no problems with the expression vectors, cells, transfection efficiency, growth conditions or other parameters which affect any comparative analysis of 350 amino acid VEGF-2 and 419 amino acid VEGF-2 precludes making any meaningful conclusions.

The Alitalo Declaration II Fails to Recognize that the 350 Amino Acid VEGF-2 Is Provided by the HGS Patent Specification

27. Alitalo Declaration II purports to provide a sequence analysis of the VEGF-2 clone deposited with the American Type Culture Collection as ATCC Accession Number 75698. Based on his analysis, Dr. Alitalo alleges that the deposited clone does not have the complete 350 amino acid sequence when compared to the sequence set forth in Figure 1 of the HGS patent specification. However, in my opinion given that Figure 1 of the HGS patent specification does contain the complete 350 amino acid coding sequence, as

even Dr. Alitalo agrees, I fail to see the criticality of Dr. Alitalo's sequence data.

28. Power Declaration II clearly demonstrates that even assuming *arguendo* that the DNA deposited in ATCC Deposit No. 75698 was missing the first 24 amino acids ("the 326 amino acid form of VEGF-2"), both the 350 amino acid form and the 326 amino acid form are processed to the same molecular weight species as compared to the 419 amino acid form of VEGF-2. When expressed as taught by the HGS patent specification, the 350 amino acid form and the 326 amino acid form are both processed to a protein which resolves as a doublet at approximately 30 kDa, as does the 419 amino acid form. (Power Declaration II at ¶ 31). I note that the experimental design of Power Declaration II includes appropriate controls to address transfection efficiencies, sequence confirmation of expression constructs, and controls eliminating any disparities in cell densities or growth conditions, as would be the standard practice of a skilled molecular biologist.

29. Furthermore, the results presented in Power Declaration II clearly evince that even if the DNA deposited in ATCC Deposit No. 75698 did not contain the complete nucleotide sequence provided in Figure 1 of the HGS patent specification, I or a skilled molecular biologist, would have been able to generate the complete 350 amino acid coding sequence based on the nucleotide sequence provided in Figure 1 of the HGS patent specification in combination with standard recombinant techniques known as of March 1994. An example of an approach I could possibly use is the same approach actually used in Power Declaration II, that is, using the sequence provided in Figure 1 of the HGS patent specification, a double stranded oligonucleotide containing the missing sequence is synthesized and is ligated to the DNA obtained from the ATCC, thus recreating the coding sequence of the 350 amino acid form. Alternatively, the template for the PCR reaction could have been obtained by reverse transcription, a technique readily available in March, 1994, using RNA

from sources provided by the HGS patent specification, such as, early stage human embryo osteoclastomas, adult heart or several breast cancer cell lines (*see*, the HGS patent specification at page 5, lines 19-24, Example 1 and Figure 5). Additionally, I or a skilled molecular biologist, could follow the teachings of the examples provided in the HGS patent specification and obtain the nucleotide sequence encoding either the 419 or the 350 amino acid form of VEGF-2 from a cDNA library derived from early stage human embryo week 9 (*see*, the HGS patent specification at page 5, lines 19-24).

CONCLUSIONS

30. In sum, the experiments reported in Alitalo Declaration II are not designed to accurately assess the expression of 350 amino acid VEGF-2 as taught in the HGS patent specification. I additionally note that Dr. Alitalo's mischaracterization of the expression profile of VEGF-2 as taught in the application, based on the data generated from experimental design without basis in the teachings of the application is exaggerated by the additional flaws introduced into his experimental protocol. Finally, I note that I am in agreement with Dr. Alitalo's and Dr. Heldin's comments presented in the course of obtaining his own VEGF-2 patents which reflect Dr. Alitalo's recognition that the 350 amino acid VEGF-2 can be naturally processed to its mature form and that the molecular weight and the amino acid sequence of the resulting processed mature form of VEGF-2 are intrinsic and natural properties of that molecule.

AND I declare further that all statements made in this Declaration of my own are true in every particular, and that all statements made on information and belief are believed to be true.

Sworn by the said Dr. Stuart Aaronson, Stuart Aaronson at New York, New York, on this 22nd day of March 2002; before me Gean Rotmistrenko

Notary Public

GEAN ROTMISTRENKO
Notary Public, State of New York
No. 41-4778718
Qualified in Queens County
Certificate Filed in New York County

SEQUENCE ANALYSIS DEMONSTRATING VEGF-C AND VEGF-2 ARE THE SAME MOLECULE

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VEGF-C      MHLLGFFSVACSLLAAALLPGPREAPAAAAAFESGLDLSDAEPDAGEATAYASKDLEEQL   60
VEGF-2      MHSLGFFSVACSLLAAALLPGPREAPAAAAAFESGLDLSDAEPDAGEATAYASKDLEEQL
                 *

VEGF-C      RSVSSVDELMTVLYPEYWKMYKCQLRKGGWQHNREQANLNSRTEETIKFAAAHYNTEILK  120
VEGF-2      RSVSSVDELMTVLYPEYWKMYKCQLRKGGWQHNREQANLNSRTEETIKFAAAHYNTEILK

VEGF-C      SIDNEWRKTQCMPREVCIDVGKEFGVATNTFFKPPCVSVYRCGGCCNSEGLQCMNTSTSY  180
VEGF-2      SIDNEWRKTQCMPREVCIDVGKEFGVATNTFFKPPCVSVYRCGGCCNSEGLQCMNTSTSY

VEGF-C      LSKTLFEITVPLSQGPKPVTISFANHTSCRCMSKLDVYRQVHSIIRRSLPATLPQCQAAN  240
VEGF-2      LSKTLFEITVPLSQGPKPVTISFANHTSCRCMSKLDVYRQVHSIIRRSLPATLPQCQAAN

VEGF-C      KTCPTNYMWNNHICRCLAQEDFMFSSDAGDDSTDGFHDICGPNKELDEETCQCVCRAGLR  300
VEGF-2      KTCPTNYMWNNHICRCLAQEDFMFSSDAGDDSTDGFHDICGPNKELDEETCQCVCRAGLR

VEGF-C      PASCGPHKELDRNSCQCVCKNKLFPSQCGANREFDENTCQCVCKRTCPRNQPLNPGKCAC  360
VEGF-2      PASCGPHKELDRNSCQCVCKNKLFPSQCGANREFDENTCQCVCKRTCPRNQPLNPGKCAC

VEGF-C      ECTESPQKCLLKGKKFHHQTCSCYRRPCTNRQKACEPGFSYSEEVCRCVPSYWKRPQMS  419
VEGF-2      ECTESPQKCLLKGKKFHHQTCSCYRRPCTNRQKACEPGFSYSEEVCRCVPSYWQRPQMS
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The consensus line:
* = Indicates substitutions that are neither conserved nor semi-conserved.
: = indicates conserved substitutions.
. = indicates semi-conserved substitutions.

AARONSON DECLARATION

APPENDIX I

FILE HISTORY
U.S. PATENT NO. 6,245,530
ISSUED JUNE 12, 2001

1. Application as filed
   July 28, 1989

2. Office Action
   2/1/90

3. Response to Office Action
   5/7/90

4. Information Disclosure Statement
   5/7/90

5. Office Action
   9/4/90

6. Response to Office Action
   2/8/91

7. Office Action
   5/3/91

8. Notice of Appeal From the Preliminary Examiner to the Board of Patent Appeals and Interferences
   10/31/91

9. Revocation and Appointment of Attorney
   11/26/91

10. Power of Attorney to Associate Attorney and Change of Address
    4/6/92

14. Information Disclosure Statement
    3/21/97

15. Information Disclosure Statement
    4/16/97

16. Office Action
    5/25/97

17. Amendment and Reply
    11/26/97

18. Transmittal of Powers of Attorney/Change of Inventors Address
    2/24/98

19. Office Action
    3/24/98

20. Amendment and Reply
    7/23/98

21. Office Action
    10/8/98

22. Supplemental Information Disclosure Statement
    7/26/99

23. Supplemental Information Disclosure Statement
    10/26/99

24. Office Action
    4/4/00

25. Associate Power of Attorney
    6/22/00

26. Office Action
    6/29/00

27. Amendment and Reply
    8/4/00

28. Amendment After Allowance/Request for Approval of Drawing Changes
    1/24/01

29. Issue Fee Transmittal
1/24/01